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STREPTOMYCIN THERAPY FOR CERTAIN INFECTIONS OF INTESTINAL ORIGIN*

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SEVERAL reports have already been published concerning the laboratory and clinical investigations on the efficacy of streptomycin in various infections carried out in Army hospitals under the auspices of the Surgeon General during the past eighteen months.[1-5] The purpose of the present communication is to enlarge on and bring up to date experience with treated infections of intestinal origin. The Army series is compared with the cumulative experience in these infections as recently reported by the Committee on Therapeutics and Other Agents of the National Research Council.[6]

BRUCELLOSIS

The most recent report of the Committee revealed that, as of September, 1946, a total of 45 patients with brucellosis had been treated with streptomycin, of whom 15 showed no alteration in the course of the illness.[6] The other 30 patients showed a decrease in fever while under treatment. Two relapses occurred in the 29 patients in this group who were followed up from three to eight weeks. Five of the 30 apparently improved patients received less than 3 gm. of streptomycin daily, and 25 received 3 or 4 gm. daily for periods varying from five to sixteen days. Of the 15 unimproved patients, 5 received from 3 to 4 gm. daily, and the others received 2 gm. daily.

All cases investigated by the National Research Council were acute and culturally proved. Insufficient time has elapsed to permit a determination of the effect of streptomycin on the relapse rate in brucellosis, but its effect in the acute disease is evidently not pronounced. It was the opinion of the Committee that if streptomycin is used in brucellosis, the minimum dose should be at least 4 gm. daily for fourteen to twenty-one days.

Up to the present time 25 cases of brucellosis have been studied in the Army streptomycin program, of which 12 were acute and 13 chronic. The disease was classified as chronic when fever and symptoms had continued for a year or more. Blood cultures were positive for Brucella in 11 of the 12 acute cases, and the organisms were found to be sensitive to 0.5 to 1.0 microgm. per cubic centimeter of streptomycin. A bacteremia was present in 2 of the chronic cases. Most of the patients had positive skin reactions to killed Brucella organisms, and Brucella agglutinins in titers higher than 1:80 were obtained in the blood in all cases. Titers ranged from 1:320 to 1:5120 in the acute cases and from 1:80 to 1:1280 in the chronic cases.

Because these patients were observed over a period of fourteen months there was considerable variation in the amount of streptomycin that they received, as well as in the duration of treatment. By present standards some received too small doses for too short a time for beneficial results to be anticipated. The largest daily dose was 6 gm., — in 2 cases, for a fourteen-day period, — but some patients received only 1 or 2 gm. daily for ten days. The intermittent intramuscular route was used in all cases.

The over-all results, regardless of whether large or small doses were used, indicated clearly that streptomycin is not effective in brucellosis. In the acute type of disease bacteremia disappeared in some, although not in all, cases while the drug was being administered, but recurrences were frequent, occurring in 5 cases. The relief of symptoms and improvement in appetite that some patients experienced under treatment could quite as well have been due to expected natural remissions and to psychologic factors as to streptomycin.

The following cases demonstrate typical responses to streptomycin therapy in brucellosis.

CASE 1. A 28-year-old Army officer had been in good health until December 12, 1945, when, during a leave, he developed chills, fever, night sweats, headaches, asthenia and anorexia. After ineffective treatment with sulfadiazine he was admitted to an Army regional hospital on January 4, 1946. When questioned, he stated that he was not aware of having ingested raw milk or dairy products made from raw milk.

Physical examination showed a wan and listless man. The only other positive findings were a reddened pharynx and a palpable but not tender spleen.

Examination of the blood revealed a white-cell count of 6000, with 61 per cent lymphocytes. A blood culture grew colonies of Brucella.

Between January 4 and 15 asthenia and anorexia persisted, and there were daily afternoon temperature elevations to 101 and 102°F. Sulfadiazine was begun on January 15

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This project was carried out as a part of the study being made under the direction of the Army Medical Research and Development Board, Office of the Surgeon General.

and discontinued on January 27, after 68 gm. had been administered. The temperature, which had fallen to normal, began to rise again on February 12, when a second course of sulfadiazine was begun, in combination with subcutaneous injections every 3rd day of a suspension of heat-killed Brucella. Blood cultures remained positive, and the patient showed no improvement. The combined therapy was discontinued on March 11, and 1 week later the patient was transferred to Halloran General Hospital.

Streptomycin therapy was begun on March 21 by the intramuscular route in doses of 0.5 gm. every 4 hours. At the end of 21 days penicillin in doses of 40,000 units was added to each injection for an additional 5 days. Transfusions of citrated blood were also given. A mean blood serum level of 16 microgm. per cubic centimeter was maintained, which, since the organism was sensitive in vitro to 0.5 microgm. per cubic centimeter, meant that the blood level was many times the concentration required for bacteriostasis in vitro.

Throughout the period of treatment, there had been inconstant albumin and casts in the urine, and 24 days after treatment had been begun, the patient complained of dizziness and had difficulty in focusing his gaze. The streptomycin was discontinued 48 hours later. For the next 8 days the temperature rose only to 100°F. daily, but on April 24 the elevations assumed the former level of 102 and 103°F. On April 29 the blood culture was again positive. The organisms recovered were inhibited by 0.5 microgm. of streptomycin per cubic centimeter, just as they had been originally.

On May 21 streptomycin was resumed in the same intramuscular doses as had previously been given, and on the assumption that the drug had not previously reached all foci of infection, it was also given by mouth in daily doses of 2 gm. At the end of 1 week no obvious improvement had occurred under this regime. Streptomycin was then discontinued by mouth but was continued by the intramuscular route, and the patient was given, in addition, 6 gm. of sulfadiazine daily. The temperature fell rapidly during the next 14 days, and as of December 1, there had been no recurrence. The patient felt well, had an excellent appetite and was gaining weight. No remission of similar length had occurred since the onset of illness, and it is believed that observation has been carried out for a sufficient length of time to regard the patient as apparently cured.

Case 2. A 30-year-old bacteriologist was hospitalized on July 27, 1945, complaining of "high fever" and "weakness" for the preceding 48 hours. These symptoms had followed a mild episode of diarrhea. Temperature elevations persisted after hospitalization, and blood cultures on three different occasions were positive for Brucella, which was determined to be sensitive in vitro to 1 unit of streptomycin per cubic centimeter. Streptomycin therapy was begun on August 11, the patient receiving 0.2 gm. intramuscularly every 4 hours for 10 days. The fever subsided by lysis, and the temperature reached normal on the 8th day of treatment. Three days later a thrombophlebitis developed in the deep veins of the left leg but gradually subsided. An episode of pneumonia, which began on September 8, responded promptly to penicillin.

During September two febrile episodes were associated with malaise and generalized lymphadenopathy, and a third episode of the same kind occurred in October. At that time a blood culture was again positive for Brucella. Streptomycin therapy was resumed, the patient receiving 0.33 gm. by the intramuscular route every 4 hours for 10 days. The febrile course was completely unchanged, and there were daily temperature elevations to 102°F., but blood cultures became negative. The streptomycin level in the blood reached 16 units per cubic centimeter. Twenty-four hours after treatment had been discontinued the temperature returned to normal, but after a short interval it again became elevated. Since streptomycin was obviously of no value, it was not resumed. The patient has continued to run a course typical of undulant fever.

The course in Case 2 is characteristic of the uniform lack of response to streptomycin therapy in all acute and subacute cases of brucellosis. Case 1 is likewise typical of the response in acute cases: the blood cultures tended to remain positive regardless of the dose of streptomycin given and the route of administration. These results are what might be expected. Brucella infections are characterized by the distribution of organisms through the lymphatic system and the blood stream, with localization in the gall bladder, spleen and lymph nodes, as well as in other structures. Previous studies on the disposition of streptomycin given parenterally, in cases in which death occurred in the course of treatment, indicate that the drug does not reach the lymph nodes in assayable amounts, whereas only small amounts can be recovered from the parenchyma of the spleen.[2] Levels in bile from the gall bladder and from the common duct are about a quarter as high as that in the blood serum. These observations are in accord with those of Reimann, Price and Elias[7] and Nichols.[8]

A remarkable feature of Case 1 is the fact that the susceptibility of the organisms to streptomycin, as shown by the blood culture, was in no way altered after twenty-six days of intensive therapy. Two possible explanations were postulated: that the drug did not reach all foci of infection, and that the organisms were unique in not developing the expected drug-fastness usual under these circumstances. On the assumption that the first explanation was correct, streptomycin was given by mouth, in addition to its administration by the intramuscular route, but without effect on the course of the disease. On the assumption that the organisms were unique the culture was sent to the Merck Institute at Rahway, New Jersey, to determine whether fastness to streptomycin in vitro could be developed. The studies led to the conclusion that the organism isolated in this case followed the usual pattern and had become habituated to increasing concentrations of the drug. The findings therefore support the hypothesis that streptomycin does not reach the foci of infection in brucellosis in lethal concentrations.

In Case 1 the prompt response to the combined administration of streptomycin and sulfadiazine, after treatment by streptomycin alone had had no effect on the acute disease, led to the similar combined treatment of another patient, who had also shown no response to streptomycin alone. A similarly prompt and favorable response was obtained, and the patient has remained well over a six-month period of observation. It is still too early to state that permanent arrest of the disease was obtained in either case, but the combined method of treatment seems to deserve further trial as part of the general therapy of brucellosis. If it is employed, it is recommended that the dose of streptomycin be 0.5 gm. intramuscularly and the dose of sulfadiazine 1 gm. orally every four hours, and that treatment be continued for fourteen days or more.*

*Since the completion of this paper, 4 additional patients with the acute or bacteremic form of undulant fever have received combined streptomycin and sulfadiazine therapy for an average period of seventeen days. Three had a prompt remission, which has been sustained. In the fourth, a twenty-four-year-old woman, from whom Brucella could not be cultured, this therapy had no effect on the course of the disease.

Typhoid and Paratyphoid Fevers

Schatz and his associates[9] were the first to report that streptomycin has a potent bacteriostatic action in vitro on the typhoid-dysentery-Salmonella group of pathogens, an observation that our studies subsequently confirmed.[2] A wide variation in range of sensitivity occurred when large numbers of the same species were examined. It is of considerable importance, however, that over 80 per cent of the organisms were found to be inhibited by 16 microgm. per cubic centimeter, which indicates that the administration of 0.4 gm. of streptomycin intramuscularly every four hours is sufficient to inhibit in blood serum the majority of the bacteria tested, since this dosage maintains the necessary blood level of the drug.

The fact that streptomycin is poorly absorbed from the gastrointestinal tract and is not inactivated by the contents of the bowel suggests that its oral use in certain susceptible infections is logical and useful. The oral administration of 4 gm. daily by mouth causes 0.01 to 0.02 gm. per gram of feces to appear in the stools and rapidly eliminates gram-negative bacteria from the bowel.[7]

The clinical experiences reported in the literature in typhoid and paratyphoid fevers are unfortunately somewhat at variance with results obtained in the laboratory.[6–8] In the 51 cases of typhoid fever studied by the National Research Council[6] doses of streptomycin varying between 1 and 5 gm. were given daily for five to nineteen days; the majority of patients received 4 gm. daily for seven or eight days. Results were reported according to the time at which treatment was begun. In 18 of 28 cases in which treatment was begun before the eighteenth day of illness the temperature was normal before the twenty-eighth day, but in the other cases elevations persisted for periods ranging from twenty-nine to fifty-six days. In 25 cases in which treatment was begun after the eighteenth day temperature elevations persisted for twenty-eight days or more. In 1 case in which treatment was begun on the eighth day of illness the temperature was normal by the twelfth day; the blood culture became negative during treatment, but the stools were still positive a month after therapy had been discontinued. In 15 cases the oral as well as the intramuscular route was used, without apparent difference in results.

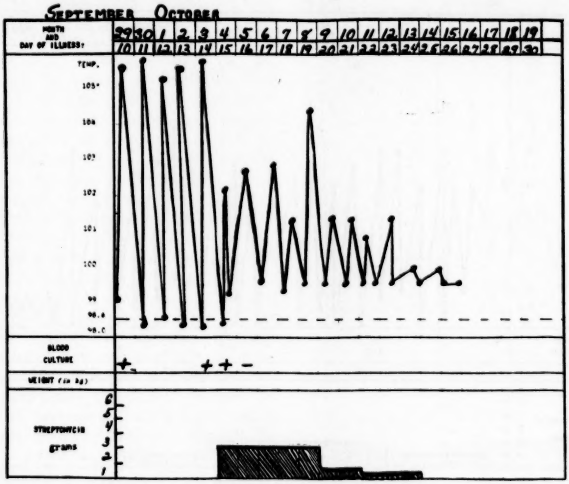

Figure 1.

This patient, a twenty-eight-year-old woman, presented the classic signs and symptoms of typhoid fever, confirmed by positive blood and stool cultures. She derived no benefit from parenteral streptomycin therapy. The effectiveness of the drug administered orally is debatable, since the organisms were reported resistant in vitro.

The Committee reported that the number of patients treated was insufficient to determine whether the fatality rate in typhoid fever could be reduced by the use of streptomycin and believed that to date no evidence was at hand to indicate that streptomycin in doses of 4 gm. daily could shorten the course of the disease. An interesting proof of this conclusion was supplied by the coincidence that the sister of a patient in the streptomycin-treated group developed typhoid fever simultane-

ously and that her course, without treatment, was identical with that of her sister, who had had treatment with streptomycin beginning on the fourteenth day and whose temperature had reached normal on the twenty-fourth day. The Committee pointed out the necessity of determining whether an earlier beginning of treatment (within the first seven days of illness) could shorten the duration of typhoid fever.

To date, results in 6 patients with acute typhoid fever, 3 typhoid carriers and 2 patients with paratyphoid infections in the Army streptomycin program have been reviewed. The diagnosis in the acute cases was established by the culture of typhoid bacilli from the blood and the stools in every case and from the urine in 1.

Three of four strains of typhoid bacilli recovered in the acute infections were inhibited in vitro by 8 microgm. of streptomycin per cubic centimeter, but the fourth strain proved drug-fast. All patients received from 2 to 4 gm. of streptomycin daily for periods varying from eight to seventeen days. The combined oral and parenteral route was used in 3 cases, and the parenteral route alone in the other 3 cases. The accompanying charts (Fig. 1–3) illustrate the diversity of the temperature response in relation to the dosage and schemes of dosage, as well as the effects of therapy on recovery of the etiologic agent from the blood and feces.

One patient died on the fourteenth day of therapy, presumably as the result of peritonitis from perforation of a Peyer's patch, which had occurred eleven days before the initiation of streptomycin therapy and which was followed by pneumonia. No autopsy was obtained.

Two of the typhoid carriers, both of whom were asymptomatic, received combined oral and systemic streptomycin therapy in doses of 4 and 2 gm. respectively for a period of ten days. In both cases typhoid bacilli were still present in the feces after treatment. The remaining carrier had developed periostitis and osteitis of the right tibia four months after apparent recovery from typhoid fever. Typhoid bacilli were aspirated from the lesion and were also recovered from material obtained by biliary drainage. The diagnosis of typhoid osteitis was thus confirmed, and the carrier state established. Streptomycin was given for ten days in doses of 2.4 gm. daily, after which the periostitis subsided and the symptoms disappeared. Four months later there was no clinical or roentgenologic evidence of infection of the bone, the Widal test became negative, and repeated cultures of urine, feces and bile showed no growth. In this case the disappearance of typhoid bacilli from the bile and from the lesion in the tibia was coincident with the administration of streptomycin.

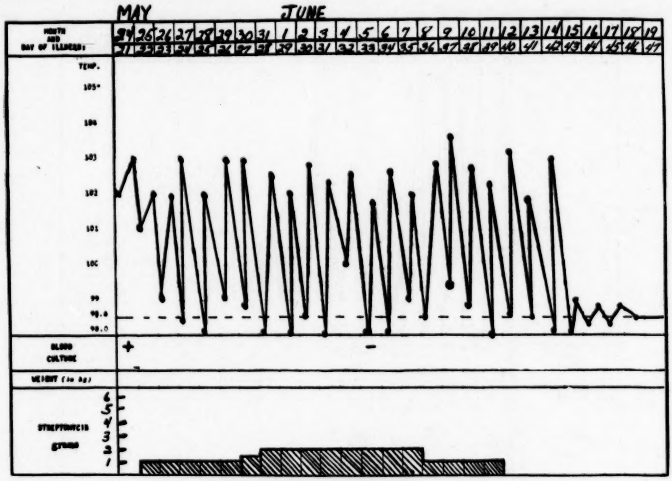

FIGURE 2.

This patient, a twenty-year-old woman, who had been immunized against typhoid fever three years before, developed severe typhoid septicemia with a toxic psychosis. Streptomycin therapy had no observable effect on the course of the illness.

In the following case streptomycin was apparently of value after sulfaguanidine had had no effect.

CASE 3. A 25-year-old soldier was hospitalized after an illness of 5 days characterized by headache, nausea, diarrhea, abdominal pain and fever. *Salmonella paratyphi* was isolated from the stools but not from the blood. The administration of sulfaguanidine did not affect the course, and on the 10th day of the illness streptomycin was begun in oral doses of 0.5 gm. every 4 hours. Eighteen hours after the first dose the diarrhea and tenesmus abated, and the temperature fell to normal. A total of 4 gm. (eight doses) was given. The patient continued to make an uneventful recovery and has remained well over a 1-month period of observation.

The results of streptomycin therapy in the 6 cases of acute typhoid fever were disappointing. In only 1 case did the fever end within a sufficiently short time and recovery follow in such a manner as to suggest that the drug was responsible for the favorable outcome. It is perhaps significant that in this apparently successful case the patient, a five-year-old child, received the dosage usually given to an adult (Fig. 3), which means that he received approximately three times as much streptomycin as any of the other patients were given. Both the oral and the parenteral routes were used. In the other 2 cases in which sensitivity to the organism was established streptomycin therapy was apparently without effect, and it is assumed that the active foci of infection were not reached. The efficacy of streptomycin in the remaining case is equivocal, since the treatment was begun when the disease was at the stage when recovery is ordinarily expected. As noted above, streptomycin by combined oral and systemic administration is theoretically the ideal treatment for enteric fever. The usual effects from systemic administration might be expected, and oral administration, because the drug is poorly absorbed from the gastrointestinal tract and is not inactivated in it, rapidly sterilizes the bowel of susceptible gram-negative bacilli. Published results of such combined treatment, however, are inconclusive and disappointing, as in our small series.

In 2 patients who were typhoid carriers streptomycin failed to eliminate typhoid bacilli from the feces. In a third carrier disappearance of typhoid bacilli from the bile and from a bone lesion coincided with the administration of streptomycin and may be attributed to its use. The administration of streptomycin was followed by a promptly favorable response and complete recovery in 1 patient with a paratyphoid infection.

ACUTE GASTROENTERITIS AND ENTEROCOLITIS

It is now quite well established that beneficial effects in varying degrees are obtained in bacillary dysentery by the use of sulfadiazine and sulfasuxidine but that these drugs are apparently of no value in Salmonella infections. Penicillin is not effective in the treatment of bacillary dysentery. The acute dysenteries respond promptly to chemotherapy. Chronic infections and the carrier state of Shigella dysentery require larger doses of the sulfonamides for longer periods before optimum results are secured. Failures of therapy, relapses and the development of the carrier state can be variously attributed to late institution of therapy, premature termination of therapy, insufficient dosage and the presence of drug-resistant bacteria.

The development of a new chemotherapeutic agent — especially one that is less toxic than the sulfonamides, can be used in smaller doses and is even more effective in the treatment of gastrointestinal infections — naturally commands attention. Streptomycin seems to fulfill these criteria. Studies indicate that it is absorbed from the gastrointestinal tract in only small quantities, that it is excreted with the feces and that, as it is passed along to the rectum, it inhibits the growth of bacteria susceptible to it. The oral administration of 2 to 4 gm. daily alters the flora of the alimentary tract, especially the gram-negative bacteria, within forty-eight hours (Fig. 4). To date we have not observed or seen reported in the literature toxic manifestations following the oral administration of streptomycin. Its use in disease of the gastrointestinal tract therefore seems indicated, especially as a substitute for the sulfonamides if in any case

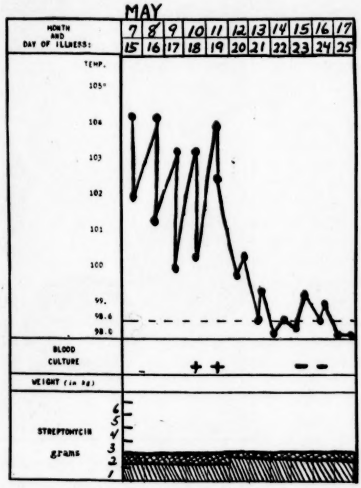

FIGURE 3.

This five-year-old boy began to receive streptomycin therapy in large (adult) doses on the fifteenth day of his illness. Blood and stool cultures were negative within twenty-four hours after therapy was begun, and the temperature reached normal eight days later.

they prove unsuitable by reason of ineffectiveness, toxicity, sensitivity of the patient or unavailability.

The most recent communication of the National Research Council[6] reported 2 cases of Shigella dysentery and 26 cases of Salmonella infection treated with streptomycin. Both patients with Shigella dysentery had previously been treated with sulfonamide drugs without result. Streptomycin, in a dosage of 1.5 gm. daily by the intramuscular route for five days, was begun in the third month of illness in 1 case and in the fifth month in the other. Stool cultures were positive in both cases before treatment and negative afterward. The period of follow-up observation was a month in 1 case and nine days in the other. Among the 26 patients with Salmonella infections 10 recovered under treatment, 2 improved under treatment and later recovered, 6 showed no improvement, and 8 died, 2 of whom had shown transient improvement in the course of treatment. Of the 19 patients with enteric involvement alone, 8 recovered, 7 were uninfluenced by treatment, and 5 died — 1 of mesenteric thrombosis four weeks after treatment had been completed. Of the 5 patients in this group with bacteremia when streptomycin therapy was begun, 3 recovered and the blood cultures became negative. The other 2 continued to have positive cultures and eventually died.

Seven of the 26 patients reported by the Council had enteric infections complicated by other conditions. Three had involvement of the lungs. Two of these had positive blood cultures when treatment was begun; 1 recovered, and 1 died. The third patient had negative blood cultures when treatment was begun and showed clinical improvement. Of 2 patients with Salmonella meningitis 1 recovered under treatment, and 1, after transient improvement, died of hydrocephalus secondary to the infection. One patient was comatose when treatment was begun and died three days later; autopsy showed a complicating encephalitis. In a case in which the Salmonella infection was superimposed on ulcerative colitis three courses of streptomycin resulted in transient improvement, which was followed on each occasion by a recurrence of symptoms.

The average dose of streptomycin in these 26 cases was 3 gm. for seven days. Treatment in 13 cases was started on the third to the sixth day of illness, and in the remainder from the seventh to the twenty-eighth day. When streptomycin therapy

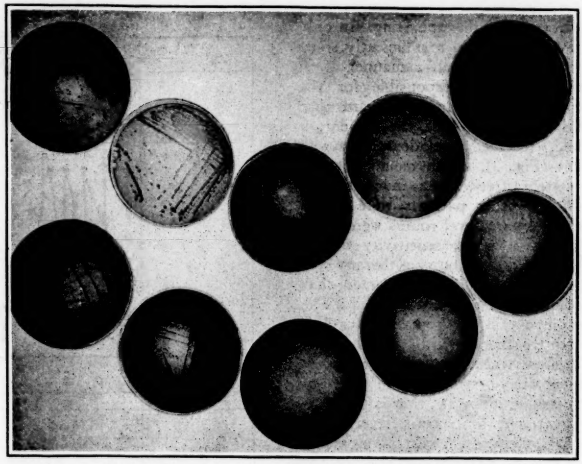

FIGURE 4. *Effect of Oral Streptomycin on Fecal Flora.*

These plate cultures of colostomy swabs were made at twenty-four-hour intervals; they show the effect of the ingestion of 0.5 gm. of streptomycin every six hours. The drug effectively suppresses the fecal flora in forty-eight hours, but sterilization is not achieved, since it does not inhibit yeasts, fungi and certain gram-positive organisms, including Clostridia, which suggests that it might be desirable after forty-eight hours to combine oral penicillin therapy with streptomycin therapy. The last plates, made forty-eight hours after the drug had been discontinued, indicate that bacteriostasis was still present.

was begun after the eighth day of illness only 1 patient recovered.

The conclusion of the Council was that the high mortality in this series could be accounted for by the varying sensitivity to streptomycin of the various strains of Salmonella organisms, with the localization of the infection and complications of other diseases as possible additional factors. In view of the high mortality the recommendation was made that in Salmonella infections maximum doses of streptomycin be used as early as possible in the illness and that treatment be continued for at least fourteen days.

Bacillary Dysentery

Our experience with streptomycin therapy in bacillary dysentery includes 10 cases. The infecting organism was *Shigella paradysenteriae* (Sonne) in 4 cases and in 6 various subtypes of *Sh. paradysenteriae* (Flexner). Five patients were treated during the first attack of illness, and the remainder after previous episodes of diarrhea. In almost every case the patient had previously been treated with either absorbable sulfonamides, such as sulfadiazine and sulfathiazole, or the unabsorbable variety, such as sulfaguanidine and sulfasuxidine, or both. Streptomycin was given in doses of 1 to 4 gm. daily for periods ranging from one to twelve days. The drug was administered orally in 2 cases, parenterally in 6 and in combination in 2.

In nearly every case the results were good to excellent. The causative bacilli disappeared from the feces, and symptomatic improvement was concomitant. The response was most dramatic in cases in which treatment was begun in the first attacks, and in patients with recurrent diarrheas who received combined oral and parenteral therapy amounting to 4 to 6 gm. daily for twelve days or longer. No case of relapse has been recorded in periods of observation ranging from one to four months.

The following case is presented as typical of a successful result:

CASE 4. A 21-year-old medical corpsman, on duty in the Pacific, had been well until November 15, 1944, when he began to suffer from abdominal cramps and diarrhea. Treatment with paregoric, bismuth and sulfaguanidine did not improve the symptoms. On admission to a station hospital on December 26 he was found to have hookworm ova (*Necatur americanus*) in the stools, but appropriate treatment produced no improvement in the original symptoms. On January 11, 1945, he was transferred to a general hospital, where he remained for 11 weeks. Treatment for hookworm was again carried out. The patient was relieved of cramps, although the diarrhea persisted, and was eventually returned to limited duty. On July 21 he was readmitted to the general hospital for recurrence of cramps and was returned to the United States, where he was admitted to an Army general hospital on October 5. At that time he was having four or five loose stools daily. Stool cultures showed *Shigella paradysenteriae* (Flexner V and Z). Treatment with sulfaguanidine followed by sulfadiazine produced no results, and streptomycin therapy was begun on February 19, 1946, in doses of 0.25 gm. every 4 hours and was continued for 10 days. On the 7th day of treatment the temperature rose to 101 and on the 9th day to 103°F. On the 10th day a rash on the trunk was observed. The rash disappeared and the temperature fell to normal 24 hours after treatment had been completed. In the course of treatment the stool culture became negative, and the patient had formed stools for almost the first time since the beginning of the illness. He was well at the end of a 3-month period of observation. No definite cause for the temperature elevation or the rash that developed in the course of treatment could be found, and both were attributed to a possible allergic reaction to streptomycin or to a possible impurity in the product.

Salmonella Infections

Ten patients with enteric infections harboring Salmonella organisms in the stools received streptomycin therapy. Two had acute gastroenteritis and enterocolitis with blood cultures positive for Salmonella when treatment was begun. Combined oral and intramuscular streptomycin therapy for seven days resulted in elimination of the organisms from the blood stream and the feces, with relief of symptoms. No relapses were recorded. Three infants with severe diarrhea and Salmonella organisms in the stools were given streptomycin orally alone, in daily doses of 100 mg. per kilogram of body weight for four to seven days, with attendant decrease in fluidity and number of stools and cultures negative for Salmonella for a follow-up period of three weeks. The remaining 5 patients had acute exacerbations of recurrent diarrhea, as well as stool cultures growing Salmonella organisms. Two patients were treated with streptomycin orally, without effect. Oral therapy was then combined with intramuscular streptomycin in 1 case, and three stool cultures became negative and remained so. Three patients with Salmonella organisms superimposed on a chronic enterocolitis received both oral and systemic streptomycin for a total dosage of 4 to 6 gm. for ten to fourteen days. These patients obtained symptomatic relief during treatment, and cultures became and remained negative for Salmonella. Mild abdominal cramps and loose stools persisted, however, even though the Salmonella organisms did not reappear in follow-up cultures.

In the evaluation of these results of streptomycin therapy it must be borne in mind that acute bacillary dysentery and salmonellosis are frequently self-limiting diseases. On the other hand, the results in this small series of cases suggest that the therapeutic effect of this method is favorable. The observations reported are comparable to those made when the absorbable and nonabsorbable sulfonamides are used in susceptible cases. The results were usually favorable regardless of the method of administration employed.

Beneficial results were obtained in this series in acute infections caused by Salmonella and Shigella organisms that had proved resistant to sulfonamide therapy. Doses of 3 to 6 gm. for periods ranging from three to sixteen days are probably adequate in most cases, but the larger amounts are recommended, for periods ranging from four to ten days,

to minimize the risk of development of streptomycin resistance. Since the offending bacteria are not confined to the lumen of the bowel but may penetrate into deep crevices and mesenteric lymph nodes, the combined oral and systemic method of administration seems more rational than the use of either route alone and is recommended. Evidence to date does not suggest that, as is advisable when the sulfonamides are used, streptomycin should be withheld until normal hydration is restored. Toxicity has not been observed following oral administration of the drug.

Streptomycin therapy was tested in 2 cases of amebic dysentery and proved of no value. The dosage was 5 gm. daily for five and nine days, respectively, by the combined oral and systemic routes. The lack of results emphasizes the futility of employing streptomycin in any condition caused by organisms not susceptible to it.

Colitis

The most recent report of the National Research Council[6] includes only 1 case of ulcerative colitis on which a Salmonella infection was superimposed, as mentioned above. Three courses of streptomycin resulted in only transient improvement.

Our experience with streptomycin includes 16 cases of chronic idiopathic colitis and ileocolitis, in all of which the dysenteric disease had progressed from the acute to the chronic phase. In 1 case a culture revealed hemolytic streptococci. No causative organism could be isolated in any of the remaining cases. The diagnosis was based on the history, the symptomatology, positive roentgenologic observations, positive proctoscopic and sigmoidoscopic observations and the exclusion by proper tests of such specific conditions as bacillary dysentery, amebic colitis, tuberculous colitis, lymphopathia venereum and deficiency states.

Seven patients had chronic static disease. The 9 remaining patients were in the acute, active stage, with systemic manifestations. The lesions varied from a localized area in the most distal segment of the rectum to diffuse involvement of the entire large bowel. One patient had, in addition to colitis, a segmental ileitis for which an ileocolostomy had been performed. The 9 patients with extensive involvement were moderately to seriously ill.

All the patients had had a variety of previous treatments, including sulfonamide and penicillin therapy, with either no response or with only temporary improvement. This is in agreement with the general experience. Amelioration of symptoms has sometimes been obtained by the use of the sulfonamides and penicillin, but no significant series of cases has been reported in which lasting remissions could be directly attributed to chemotherapy.

Streptomycin was given in doses ranging from as little as 0.2 up to 2 gm. at intervals of three to six hours, by the intramuscular or oral route or by both routes, for periods ranging from four to sixty-two days. Penicillin was also given in 1 case. Improvement was considered to have occurred if there was a reduction in the number of stools, a decrease in or disappearance of blood in the stools, and relief from the concomitant symptoms of toxemia. On this basis temporary improvement was observed in all acute cases except 1 in which a hemolytic streptococcus was implicated as the etiologic agent. In the cases of chronic static disease some improvement usually occurred during therapy, but it was generally undramatic and seldom permanent. The following case is not atypical.

Case 5. A 25-year-old officer developed diarrhea in October, 1945, with bright-red blood in the stools. He was hospitalized promptly but continued to have two to fifteen bowel movements daily, many of which contained blood. Cysts of *Endamoeba histolytica* were found in the stools on a number of occasions, and significant titers (1:320) for *Shigella paradysenteriae* (Flexner Y) antibodies were demonstrated in the blood. There was positive roentgenologic and sigmoidoscopic evidence of ulcerative colitis. Courses of antiamebic drugs, sulfathiazole and penicillin, alone and in combination, failed to influence the course of the disease. Repeated transfusions of blood and plasma were necessary for correction of a marked anemia.

Streptomycin therapy was begun on May 29, 1946, in doses of 0.5 gm. orally every 3 hours and was continued for 5 days. The drug was discontinued after an increase in diarrhea accompanied by temperature elevations had developed. On June 28 a second course of streptomycin was begun in the same dosage and was continued for 14 days. The dosage employed effectively eliminated the susceptible fecal flora but had no effect on the temperature elevations and diarrhea. A third course was begun on July 29, the drug being given intramuscularly in dosages of 0.4 gm. every 4 hours for 7 days. There was no alteration in the course of the disease or in the bacteriologic findings, and streptomycin therapy was permanently discontinued.

In evaluating the results of streptomycin in colitis it is necessary to bear in mind two points: whether the streptomycin therapy is a part of the medical regimen in a case in which surgery is not required, or whether it is employed in the hope of controlling the active phase of the disease, so that resection can be more safely undertaken; and just what is expected from treatment. Whatever the objective of therapy, it is obvious that no chemotherapeutic agent can be expected to restore to normal the physiologic function of an intestine that has undergone irreversible changes and has become contracted and deformed by disease of long standing. All that any drug can be expected to accomplish under such circumstances is to control symptoms due to active infection.

The majority of patients treated in this small series derived some benefit during treatment with streptomycin, but over-all findings are contradictory and no particular optimism seems warranted; it could scarcely have been expected. The impression is gained from a study of these cases that future evaluation of streptomycin therapy should be on the basis of longer courses of combined oral and systemic administration.

Epidemic Diarrhea

The report of the National Research Council[8] apparently includes no cases of epidemic diarrhea in infants. The present study comprises 13 cases of this type of diarrhea. Eight infants were received from an Army transport, which had been the scene of an outbreak of the disease, and 4 were serious cases of nonspecific gastroenteritis complicated by dehydration, toxemia and varying degrees of malnutrition that, in 2 cases, amounted to a state of marasmus. The thirteenth patient had also had gastroenteritis, and was 1 of 3 controls; she was treated with streptomycin when her condition failed to improve under the usual treatment. No Shigella or Salmonella organisms of the usual pathogenic variety could be recovered from any of these cases. *Proteus morganii* and *Pr. vulgaris* predominated in all cases, but since these organisms are present in normal stools and tend to overgrow other bacteria readily, it is difficult to incriminate them as the etiologic agents. It is believed with reasonable certainty that no single organism was responsible for the infection in any case in the group.

Because of a lack of previous experience with streptomycin in epidemic infantile diarrhea, the first 7 infants received from the Army transport were treated with small doses of the drug. Two died, forty-eight and seventy-two hours, respectively, after the beginning of therapy, as the result of severe toxemia and central-nervous-system involvement. The remaining patients were discharged in good condition and on full diets between the fifteenth and thirtieth days after admission; hospitalization was prolonged in some cases because of extensive weight loss. All these children received daily doses of streptomycin varying from 0.1 to 0.2 gm. per kilogram of body weight at four-hour intervals over periods varying from two to ten days. The eighth patient received from the Army transport was given 0.1-gm. doses at four-hour intervals for six days. Two of 3 patients with infantile diarrhea used as controls while these 8 children were under treatment with streptomycin did well under the usual treatment. The third, after a period of improvement under the usual routine, regressed and became critically ill, but recovered after the use of large doses of streptomycin.

Two babies with nonspecific gastroenteritis associated with malnutrition and dehydration, after failure of the usual treatment, were given streptomycin in daily doses of 0.3 to 0.6 gm. per kilogram of body weight and were placed on full diets at the same time. One made a prompt and dramatic recovery. The other continued to have diarrhea and fever until the daily dosage of streptomycin was raised from 0.3 to 0.6 gm. per kilogram of body weight. Although the diarrhea was controlled and the temperature began to fall, death eventually occurred from pneumonia and heart failure. Two other infants with nonspecific gastroenteritis were treated early and vigorously with streptomycin in daily doses of 0.12 and 0.25 gm. per kilogram of body weight and showed prompt improvement. One child was discharged within twelve days, after a gain of 1 pound, 5 ounces, over a period of only eight days. When treatment was begun she was moribund, being in a state of respiratory and circulatory collapse; nervous-system involvement was manifested by convulsions, spasticity, facial paralysis, stupor and coma. When she was discharged the only residuum was a mild facial palsy.

One child, in another Army hospital, was treated by doses of 30 mg. of streptomycin orally every hour for one hundred hours. Diarrhea was controlled but recurred briefly after therapy had been discontinued. Larger doses given over a longer period might have been more promptly effective.

No conclusions regarding the value of streptomycin therapy in epidemic diarrhea can be drawn from so small a series of cases. On the other hand, it was the considered opinion of Major Irvin J. Cohen, under whom these cases were handled, that at least 4 of the 13 children are alive today because of streptomycin, which in all cases seemed to shorten the period of illness, control starvation and malnutrition and reduce the hospital stay. When a proper routine of usage has been established, a demonstrable reduction in mortality may reasonably be expected. Further studies should be conducted on infants with epidemic infantile diarrhea and nonspecific gastroenteritis by the following regimen: parenteral fluids, including blood and plasma to combat shock and restore water, electrolyte and protein balance; early oral feedings of 72 to 125 calories per kilogram of body weight if vomiting is absent; and streptomycin in adequate doses, 0.5 gm. per kilogram of body weight being regarded as the minimal daily dose. Dosages up to 1.0 gm. per kilogram of body weight should be utilized in critically ill children, regardless of age. The drug should be continued for at least a week after a satisfactory response has been obtained.

Summary

The present report enlarges on and brings up to date certain streptomycin-treated cases of intestinal origin observed in the Army streptomycin program. For comparative purposes brief statements are made concerning the report of the Committee on Therapeutics and other Agents of the National Research Council on the same types of infection.

Generally speaking, the results of streptomycin therapy in acute and chronic brucellosis were poor, although in 2 acute cases in which streptomycin therapy and sulfonamide therapy were combined apparent cures were achieved. The results in acute typhoid fever were disappointing, and in 2 of 3 typhoid carriers treatment was a failure. A patient with dysenteroid paratyphoid fever recovered

promptly. The results of treatment in enteritides due to Salmonella and Shigella organisms were generally favorable, but in nonspecific ulcerative colitis they were generally undramatic, or at least equivocal. Results in infantile diarrhea, although some deaths occurred, were usually good and sometimes dramatic.

Dosage, routes of administration and similar details are discussed, and lines of future investigation are suggested.

The conclusion continues to be warranted that in infections caused by organisms susceptible to streptomycin the results of treatment are likely to be good if the drug can be brought into contact with all foci of infection. If the organisms are not susceptible to streptomycin, treatment is without value.

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GOLD THERAPY IN RHEUMATOID ARTHRITIS*

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TREATMENT of rheumatoid arthritis with gold compounds, initiated in Europe twenty years ago, has gradually grown in favor in American medicine during the past ten years. Recently, Fraser[1] condensed the literature on chrysotherapy in this disease and noted that most observers report a favorable response in 70 to 80 per cent of patients. Short, Beckman and Bauer[2] found more than forty publications on gold therapy in the English literature up to 1946, almost all of which were favorable toward this type of treatment. Since these recent summaries are available, a review of the literature on this subject is not attempted in this report. When the publication of Short, Beckman and Bauer appeared, again raising the question of efficacy, we were engaged in reviewing six years' experience with gold treatment in the Arthritis Clinic, Indianapolis City Hospital. The results revealed in this survey seem sufficiently comparable to those reported by the Boston group to justify publication of the findings.

Treatment

The chronic nature of rheumatoid arthritis and its tendency to spontaneous improvement or exacerbation make difficult the accurate evaluation of progress. This is further complicated by the optimistic nature of many patients who are prone to symptomatic improvement with any treatment administered with a hopeful attitude on the part of the physician. Aware of its shortcomings but in the hope of providing a standard method of evaluation, we adopted a modification of the "yardstick" of Bayles and Hall.[3] To illustrate the method used, a portion of one patient's record is presented in Figure 1. As indicated in the key, four objective findings — mobility, activity of disease, static deformity and extent of involvement — are translated into a numerical value. Similarly, laboratory findings and subjective symptoms are assigned a number. The total of all six items provides an index number, with which the index obtained on subsequent examinations is compared. In the estimation of progress a change of two points in the index is considered to be significant. Hence, a value that decreases from 12 to 10 is accepted as indicative of improvement, and, conversely, a change from 12 to 14 is taken as evidence of progressing disease. The method appears to be helpful in the long-term and follow-up study necessary in the evaluation of therapy.

With the use of the index system the records of 52 patients treated with gold were examined. Five of these were eliminated at the outset because the patients had received less than 100 mg. of gold salts. The records in the remaining cases form the basis for this report. All patients had a definite diagnosis of active rheumatoid arthritis. All were adults ranging in age from twenty to sixty-four years at the time treatment was begun. There were 34 women and 13 men, representing a sex ratio of a little less than 3:1. The longest period of

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observation was six years, but all patients were followed for more than eighteen months. The stage of disease at the time treatment was initiated varied from less than two years' duration in 18 cases, or 38 per cent, to the later stages of the disease in 29, or 62 per cent. Patients with more advanced involvement had been treated elsewhere was followed, with most patients receiving 50 mg. of gold sodium thiomalate or 25 mg. of actual gold. The total amount per course has remained at 1000 mg. of the salt, but in most patients now under treatment, maintenance therapy of 25 mg. every two weeks has been continued indefinitely after a course has been completed. In addition,

NAME — L. M. HOSP. No. — 167923 BIRTH DATE — 1906

DATE	BRIEF CLINICAL HISTORY: Onset May, 1943, with painful, swollen hot left knee. Gradually progressed to involve proximal interphalanges, elbows and ankles. No previous history of joint disease.						GOLD (MG.)	INDEX
	M	A	D	E	L	S		
June, 1943	0	2	1	2	4	1	0	10
January, 1944	3	2	2	2	4	3	0	17
June, 1944	1	2	1	2	3	2	1310	11
June, 1945	1	2	1	2	4	1	1120	11
June, 1946	0	2	1	2	4	1	625	10

FIGURE 1. *Reproduction of a Patient's Chart.*

The key is as follows:

M — Mobility. 0 — *employable*; 1 — *ambulatory (able to get about alone)*; 2 — *confined to one floor, bed and chair without assistance*; 3 — *confined to bed, needing part-time assistance (able to feed self and so forth)*; 4 — *confined to bed, needing full-time assistance (helpless)*.

A — Activity of disease. 0 — *no activity (history of having had disease)*; 1 — *presence of disease but no objective signs of activity at present*; 2 — *intermittent heat, swelling and effusions in joints*; 3 — *appearance of subcutaneous nodules, persistent heat, swelling, tenderness and effusions in joints, with mild to moderate muscle atrophy and slow joint destruction*; 4 — *fulminating, rapid course of disease, with joint destruction, fever, rapid weight loss and so forth.*

D — Deformity of static nature (made on worst joint). 0 — *none*; 1 — *periarticular thickening, painless fluid or crepitus on motion*; 2 — *limitation of motion*; 3 — *subluxation*; 4 — *ankylosis or flail joint.*

E — Extent of joint involvement (percentage of joints involved). 0 — *none*; 1 — *0 to 24*; 2 — *25 to 49*; 3 — *50 to 74*; 4 — *75 to 100.*

L — Laboratory evaluation. 0 — *no abnormality*; 1 — *slight increase in sedimentation rate (Wintrobe method, +5 mm.) or slight anemia, or both*; 2 — *moderate change in sedimentation rate (+10 mm.)*; 3 — *severe change in sedimentation rate (+20 mm.)*; 4 — *extreme change in sedimentation rate (+30 mm. or more).*

S — Subjective symptoms. 0 — *none*; 1 — *intermittent mild to moderate malaise, weakness, fatigue and joint pain*; 2 — *continuous and mild to moderate for the above symptoms*; 3 — *intermittent and severe or continuous and moderate for the above symptoms*; 4 — *continuous and severe for the above symptoms.*

with the usual variety of remedies, but none had previously been treated with gold.

During the first years of chrysotherapy the customary weekly dose of 100 mg. of gold salts was given to a total of 1000 mg. per "course." Gold sodium thiomalate (Myochrysine) was the standard compound, although for about a year gold acetyl cystein was given. Since both compounds contain 50 per cent gold, they are considered comparable therapeutic agents. During the past four years, the current practice of giving lower weekly doses acetyl salicylic acid has been used freely to control pain, and application of heat to affected joints has been a daily routine with the majority of patients.

RESULTS

With classification on the basis of the total amount of gold salts administered, the results of treatment are summarized in Table 1. It is interesting that 8 patients who were given only 500 to 1000 mg. showed the greatest percentage improvement of any group — in fact, 17 per cent greater

than that in the group of 10 patients who were given more than 3000 mg. The next greatest improvement was in the 9 patients who received less than 1500 mg. This suggests that the first course of gold is the most effective, a finding noted by others.[4] It is interesting that 6 of the improved patients, 5 of those in the unchanged group, and all 7 listed as failures had been victims of the disease for less than two years. With these 18 patients as a group representing the earlier stages of rheumatoid arthritis, 33 per cent were improved, 28 per cent were unchanged, and 38 per cent

The fifth patient, a forty-two-year-old woman, developed a mild dermatitis after receiving 400 mg. of gold salts. This was not recognized as a toxic effect of gold, and treatment was continued. When 625 mg. had been given the patient rapidly developed exfoliative dermatitis. After five months' hospitalization for the skin condition, she died, the disease having been further complicated by epilepsy and latent syphilis. This fatal case must obviously be attributed to gold poisoning.

Evidences of gold toxicity were seen in 29 patients, or 62 per cent, of the entire group. Skin

TABLE 1. *Results of Treatment.*

Dosage of Gold Salt*	No. of Patients	Improvement		No Change		Failure†		Relapse after Improvement		Death		Reaction to Gold	
		No. of cases	Per-centage	No. of cases	Per-centage	No. of cases	Per-centage	No. of cases	Per-centage	No. of cases	Per-centage	No. of cases	Per-centage
mg.													
Less than 500....	7	0	0	7	100	0	0	0		2	29	5	71
500–999.....	8	4	50	4	50	0	0	1	12	1	12	7	88
1000–1499.....	9	3	33	6	66	0	0	1	11	2	22	6	66
1500–1999.....	7	1	14	3	43	3	43	0	0	0	0	3	43
2000–2999.....	6	1	17	4	67	1	17	0	0	0	0	3	50
3000 or more	10	2	20	5	50	3	30	0	0	0	0	5	50
Totals	47	11		29		7		2		5		29	
Averages			23		62		15		4		11		62

*Salt containing 50 per cent gold.
†Patient worse after therapy.

became worse with gold therapy. It is only fair to state that 62 per cent of the entire group showed no measurable change for better or for worse as a result of treatment. A possible effect of gold in preventing advance of the disease may thereby be implied.

Toxic Effects

During the six-year period 5 patients died, but only 1 fatal case seemed definitely attributable to gold toxicity. One man died at the age of sixty-seven years because of congestive heart failure three years after receiving a total of 400 mg. of gold salts. A woman died at the age of forty-five years with a questionable diagnosis of amyloidosis. She had completed a course of 1150 mg. of gold salts three years before death. Treatment had been discontinued because of an exfoliative dermatitis apparently due to gold, but she had recovered from this within six months after treatment had been stopped and two and a half years before death. A forty-two-year-old woman developed a mild dermatitis after having received 1215 mg. of gold salts. She died three months later after surgery for acute bowel obstruction. Another woman, aged sixty-three years, had received only 95 mg. of gold salts when she developed a mild purpura. Treatment was stopped, and she failed to return to the clinic. A follow-up letter six months later revealed that she had recently died, presumably of cerebral thrombosis.

reactions were observed quite frequently and were the reason for temporary or permanent withdrawal of the drug in 25 cases. In most cases only a mild pruritus or limited skin eruption was seen, and often after the skin had become normal treatment was cautiously resumed. Some of these patients were able to complete the course of therapy without further side-effects. Exfoliative dermatitis was seen in only 2 patients, and 2 others exhibited evidence of purpura. Treatment was discontinued temporarily in 2 cases because of neutropenia. Several patients showed evidence of renal irritation in the form of transitory proteinuria or microscopical hematuria. Diarrhea thought to be due to gold was occasionally observed.

Discussion

In these patients treated with gold salts the results have not approached those reported in the majority of publications on this subject. An explanation may be found in the longer period during which the patients were observed. In many cases apparent improvement was seen after treatment, but in few cases was there a lasting effect. In this report no attempt has been made to discuss separately patients who improved only to relapse, for it is believed that a period of more or less temporary relief is of little consequence in this disease.

The percentage of improvement in this series happens to be the same as the 23 per cent net

improvement reported by Short, Beckman and Bauer[2] in 35 cases. In contrast, through the use of general and orthopedic treatment, these authors obtained improvement in 52.9 per cent of a larger series of 274 cases without the risk that is always associated with gold therapy.

Summary

Forty-seven patients with active rheumatoid arthritis were observed for periods of eighteen months to six years. All received gold therapy in amounts ranging from less than 500 to more than 3000 mg. of a salt containing 50 per cent gold. Those who continued in an improved state after treatment constituted only 23 per cent of the total, whereas 62 per cent showed no appreciable change, and 15 per cent became worse.

A high incidence of toxic reactions to gold was noted, 62 per cent of patients having been involved. Although most of these side-effects were of little consequence, there were 2 cases of exfoliative dermatitis, with 1 death.

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TREATMENT OF ACUTE UREMIA BY PERITONEAL LAVAGE

Report of a Case

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THE treatment of uremia has long been directed toward symptomatic relief, healing of the underlying renal lesion and, in acute and presumably temporary cases, maintenance of life long enough to allow the kidneys to reassume their essential functions. It is toward the last objective that attempts have been made by numerous workers to supply a temporary "substitute" for the kidneys, which would maintain excretion of uremic metabolites, whose retention is fatal to the organism. In a review of the chemical changes known to occur in uremia, Harrison and Mason[1] stressed the importance of increased blood and tissue concentrations of urea, free phenols and guanidine-like substances; the depression of ionized-calcium concentrations through the accumulation of phosphate, citrate and oxalate; the debilitating effects of water and chloride deprivation, particularly on tissue proteins; the profound disturbances in acid-base balance due to loss of sodium ions and accumulation of organic and inorganic acids; and the hypothetical toxic effects of many other retained substances as yet incompletely identified. Since theoretically modifications in the equilibriums of all the substances named above might be effected by indirect contact, through a semipermeable membrane, with a solution of different composition, repeated experiments have been made to bring the circulating blood of uremic organisms into such osmotic contact with a prepared solution.

The technic of removal of diffusible substances from the circulating blood by dialysis through a celloidin membrane surrounded by various solutions of crystalloids was successfully demonstrated in 1912 by Abel, Rowntree and Turner[2] and reported in detail in 1914. In the experiments performed, measurable amounts of nonprotein nitrogenous substances were removed from the circulating blood of normal rabbits, and orally administered salicylates were recovered from the blood of dogs. In 1923 Ganter[3] reported the use of the peritoneum in human beings as a "natural" semipermeable membrane, a hypotonic solution being introduced into the abdominal cavity in an attempt to remove uremic substances from the blood. In a patient with chronic nephritis this attempt at maintaining life was unsuccessful. Thereafter, Rosenak and Siwon,[4] von Jeny,[5] Balázs and Rosenak,[6] Bliss, Kastler and Nadler,[7] Haam and Fine,[8] Seligman, Frank and Fine[9] and Abbott and Shea[10] demonstrated, in mammals rendered uremic by nephrectomy or ureteral ligation, that significant amounts of "uremic substances" could be removed from the circulating blood with temporary prolongation of life. The method generally used was intermittent injection into and withdrawal from the peritoneal cavity of various solutions approximating the crystalloid content and reaction of intercellular fluid. In a study of various solutions by Abbott and Shea[10] the most satisfactory fluid for use in dogs rendered uremic by bilateral nephrectomy was found to be Hartmann's solution with added sodium bicarbonate, monosodium phosphate, magnesium chloride and dextrose in concentrations up to 5 per cent.

Following Ganter's[3] effort to relieve uremia in a human patient by peritoneal dialysis, several attempts were made by Heusser and Werder,[11] Balázs and Rosenak,[6] Wear, Sisk and Trinkle,[12] Rhoads[13] and Fine, Frank and Seligman,[14, 15] who used various modifications in solution and technic of perfusion of the peritoneal cavity. Of the 17 patients whose cases are known to have been reported prior to the

present communication, only 2 have survived peritoneal dialysis. One was a case of "reflex anuria" with bladder calculus reported by Wear et al.[12] in which the nonprotein nitrogen was never above 71 mg. per 100 cc., and the alkali reserve was 51 vol. per cent. Since the bladder obstruction was relieved by catheterization and suprapubic cystotomy with subsequent profuse diuresis, the role of peritoneal dialysis was less clear cut in this case than in other reported cases. The other successful case reported by Frank, Seligman and Fine[13] was elsewhere compared with 3 cases treated by the same authors in which death followed the procedure.[14] This case was that of a fifty-one-year-old man with acute sulfathiazole anuria and uremia who recovered kidney function after seven days of continuous peritoneal irrigation with modified mammalian Tyrode's solution, in addition to the usual supportive measures.

The patient in the following case was treated through the courtesy of Drs. Frank and Seligman, of the Beth Israel Hospital, Boston, who made available all necessary apparatus and technical data and offered invaluable advice in the conduct of therapy.

J. A. Y., a 37-year-old single military prisoner was admitted to an Army hospital on July 8, 1946, complaining of burning abdominal and chest pain and hemorrhage by mouth, rectum and urethra, of about 3 hours' duration. A history was subsequently obtained that the soldier had been absent without leave and drinking heavily, with a markedly inadequate diet, for about 1 month and that, because of an acute situational depression, he had taken seven tablets (3.5 gm.) of mercuric chloride by mouth in a suicidal attempt. Within 30 minutes he had begun to vomit a bright, bluish-green liquid containing no undigested tablets; he was transferred to the hospital after routine emergency treatment with milk and egg white by mouth.

The family and past histories were noncontributory. Psychiatric examination throughout the hospital stay showed the patient to be emotionally unstable and immature, but not psychotic.

Physical examination revealed a well developed and well nourished man who appeared pale, prostrated and acutely ill and who was vomiting gross blood. The skin was dry, loose and sallow. There were areas of alopecia over the parietal areas of the scalp due to pre-existing fungus infection. The conjunctivas and pharynx were moderately injected. The heart and lungs were normal except for a soft systolic apical murmur; the blood pressure was 122/88. The abdomen was tense, tender and slightly distended, with marked peristaltic activity audible to the naked ear. No organs or masses were felt, owing to the marked abdominal tenderness and spasm, but on the 2nd hospital day the liver was palpated two and a half fingerbreadths below the right costal margin. There was no peripheral edema; neurologic examination was essentially negative.

Examination of the blood disclosed a red-cell count of 5,500,000, with a hemoglobin of 17.5 gm., and a white-cell count of 9850, with 89 per cent neutrophils, many of which showed toxic granulation. A specimen of urine measured 100 cc. and was grossly bloody, and gave a ++++ test for albumin and a + test for sugar (following intravenous injection of glucose); the sediment was filled with degenerated red cells. The nonprotein nitrogen was 40 mg. per 100 cc., and the carbon dioxide combining power 46 vol. per cent. A Gettler test on the vomitus and the urine showed traces of mercury.

Eight hours after the initial ingestion of mercuric chloride — during which the patient had been given milk, cream and egg white by mouth, 2000 cc. of 5 per cent glucose in physiologic saline solution and distilled water and 1 gm. of sodium thiosulfate intravenously — a supply of BAL in oil (Dimercaptopropanol, United States Army Medical Department Item 1088500[16]) had been obtained. The patient was given 10 per cent BAL in oil intramuscularly in the dosage recommended by Eagle and Longcope[17]: 350 mg. initially, 175 mg. 2 hours later, 175 mg. 4½ hours after the second dose and 175 mg. at decreasing intervals for the next 4 days. He experienced a severe subjective reaction to the first injection, with headache, dryness of the lips, constriction of the chest, burning of the urethral meatus and transitory elevation of the blood pressure to 144/110. Thereafter, there was little or no subjective reaction to the injections. Within 48 hours hematemesis had ceased, and the small, frequent stools appeared to contain old, rather than fresh, blood.

During the first 12 hours in the hospital, the patient passed a total of 110 cc. of grossly bloody urine; thereafter, he passed no urine until the 7th hospital day. He was more comfortable but developed increasing azotemia, so that on the 4th hospital day, the nonprotein nitrogen was 109 mg., the blood urea nitrogen 67 mg., the serum sodium 370 mg., and the total protein 6.5 gm. per 100 cc.; the carbon dioxide combining power was 40 vol. per cent. The cephalin-flocculation test (Hanger) was ++++ in 24 hours.

On the 5th hospital day — the 4th day of complete anuria — continuous peritoneal lavage was instituted with modified Tyrode's solution containing 2 per cent glucose, 2.9 per cent sodium bicarbonate and effective concentrations of heparin, penicillin and streptomycin. Small parallel incisions were made on the right and left lateral aspects of the abdominal wall at the level of the umbilicus; one was fitted with a stainless-steel, blunt-tipped suction nozzle for inflow, and the other with a large stainless-steel sump drain inserted well down into the pelvis, with a loosely fitting, straight suction tip laid inside the sump. Grossly bloody abdominal fluid, which gave a negative Gettler reaction for mercury, was recovered through both incisions.

The inflow and outflow tubes were fitted into the continuous-flow and suction apparatus described by Frank et al.,[14] and as much perfusing fluid as possible was run through the abdominal cavity, depending on the rapidity with which the suction apparatus could withdraw fluid and prevent painful distention. For the first 2 days of lavage, flow was satisfactory, reaching a maximum of 30 liters in the second 24 hours. Thereafter, because the patient tampered with the dressings, the inflow and outflow tubes and the regulating clamps, satisfactory perfusion was never maintained. The highest subsequent daily total was 23 liters on the fifth day; other daily rates varied from 3 to 14 liters. Peritoneal lavage was maintained as steadily as possible for 12 days; since by that time no free fluid could be aspirated through the blocked suction tube, even after removal and cleaning of the tube, lavage was discontinued.

Throughout the hospital course, supportive treatment was given with intravenous fluids, frequent transfusions and supplementary vitamins B, C and K parenterally. On the 6th hospital day a few coarse rales appeared over the left posterior lung base; the temperature gradually rose to 100°F. Penicillin given intramuscularly in doses of 20,000 units at 3-hour intervals, followed by streptomycin in doses of 0.1 gm. administered every 3 hours with the penicillin injections, caused gradual defervescence after the 11th hospital day. The patient was given deep breathing and coughing exercises, and the basal rales gradually diminished. No significant organism was found in the sputum except an apparently air-borne yeast, which was also growing in the outflow bottle of the peritoneal lavage. On the 10th hospital day, because of increasing abdominal distention and decreasing audible peristalsis, a Miller–Abbott tube was passed; this effected gradual decompression, but on the 18th hospital day the patient, while momentarily unobserved, pulled out the tube and shortly thereafter vomited small amounts of blood.

The patient voided 50 cc. of clear urine on the 7th hospital day, 32 cc. on the 9th day, and daily increasing amounts thereafter, to a maximum of 910 cc. on the 26th day. The urea nitrogen content of this urine, however, never became higher than 300 to 400 mg. per 100 cc., which was grossly inadequate to maintain nitrogen balance. The outflow from the peritoneal lavage contained urea nitrogen in concentrations roughly equal to those of the blood; no other chemical determinations were done on the fluid. The blood nonprotein nitrogen, which had risen to 109 mg. per 100 cc. before peritoneal lavage, remained in the vicinity of 100 mg. until

the 11th hospital day, when it again rose precipitously to 150 mg. per 100 cc. The blood urea nitrogen at that time was 105 mg. per 100 cc.; the carbon dioxide combining power had remained between 20 and 40 vol. per cent by virtue of daily intravenous administration of 1/6 molar sodium lactate. When peritoneal lavage was completely discontinued, azotemia increased still more rapidly: on the 25th hospital day the nonprotein nitrogen was 365 mg., the serum sodium 473 mg., and the potassium 21.4 mg. per 100 cc., and the carbon dioxide combining power 33 vol. per cent.

On the 22nd hospital day, the patient developed edema of the sacrum, scrotum and ankles; further edema was forestalled by reduction of intravenous fluid to 1500 cc. daily. He rapidly failed, with increasing drowsiness, continuing abdominal distention and a temperature of 97°F. On the 23rd hospital day a much louder apical systolic murmur was heard; no friction rub was made out at any time. From the 24th day onward the patient vomited and defecated fresh blood, and on the 26th day he appeared irrational. On the 27th day he suddenly became cyanotic while sitting up in bed and died.

Autopsy. At post-mortem examination, performed by Major Samuel Berg 6 hours after death, the abdomen was distended; there were recent surgical incisions from the insertion of tubes for peritoneal lavage. There was mild generalized edema, most marked over the pretibial regions. The greater omentum was attached to the abdominal wall and underlying viscera by many adhesions varying from thin to firm fibrous bands. There was a large quantity of blood-tinged peritoneal fluid containing flakes of fibrin. Between many coils of intestine there were pockets of thick, yellow, odorless pus, which on culture showed colonies of *Escherichia coli* and of Monilia. There was a well advanced "uremic pericarditis," with fibrinous adhesions and 30 cc. of blood-tinged pericardial fluid.

The right lung weighed 750 gm., and the left 450 gm. The bronchi were congested; there was moderate pulmonary edema, most marked in the lower lobes. There were several isolated thick-walled small abscesses.

The heart weighed 490 gm.; the musculature was extremely flabby. Measurements of the valves were within normal limits. The thickness of the left ventricle was 18 mm. About the chordae tendineae of the posterior cusp of the mitral valve there was a firm, constricting — apparently antemortem — clot, with a pencil-sized tail extending upward through the aortic valve.

The spleen was normal except for mild congestion. The liver weighed 2700 gm., and was softer than normal in consistence. The pancreas was embedded in a mass of fragile fatty material. The entire lesser peritoneal sac contained 60 cc. of turbid, brown fluid, with soft, whitish flakes.

Examination of the gastrointestinal tract revealed a plastic, brown exudate over the posterior wall of the stomach; a perforation of the stomach had apparently occurred and had subsequently been walled over by exudate. There was marked hemoglobin staining of the mucosa of the entire intestine; the mucosa was thin, and there were numerous necrotic transverse ulcerations throughout the distal duodenum, proximal jejunum and the entire colon. From the position of the ulcers and the nearby peritoneal abscesses, it was the opinion of the pathologist that perforation of the intestine had occurred in several places.

The right kidney weighed 420 gm., and the left 460 gm. When each kidney was transected, the parenchyma bulged high above the cut edge of the capsule. Both kidneys were pale throughout; the glomeruli could not be visualized grossly.

The brain weighed 1270 gm. and was grossly normal.

Microscopical examination disclosed that some alveoli of the lungs were partly collapsed; others showed emphysematous dilatation. The alveolar capillaries were markedly distended, and in sections from the lower lobes, the alveoli contained moderate numbers of erythrocytes and pigment-bearing phagocytes, as well as some small, round cells. There was marked disparity in the size of the cell nuclei of the liver. The cytoplasm was finely granular, and in places there were large, round vacuoles suggesting fatty degeneration. Many of the hepatic cells and a few of the Kupffer cells were almost filled with light-brown pigment granules. There were moderate numbers of small, round cells about the bile ducts, and in foci in the capsule of Glisson. There was extensive necrosis of the peripancreatic tissue, without changes in the pancreatic tissue itself.

The glomerular tufts of the kidneys were anemic and showed edema and desquamation of the capsule epithelial cells but were otherwise normal. The tubules showed marked changes, with no uniformity from place to place. The epithelial cells were loosely attached to the basement membrane, with some cells lying free in the lumens. Some of the tubules, singly and in groups, showed marked atrophic changes, the few epithelial cells lying haphazardly in clusters within an edematous stroma containing small, round cells and a few polymorphonuclear leukocytes. In a few places in the distal tubules, on the other hand, the epithelial cells were stratified and the nuclei varied in size, suggesting recent regeneration.

In this case peritoneal lavage was used in an attempt to maintain life for a sufficient period to allow restoration of kidney function after sudden failure. Despite survival for twenty-seven days, it is evident that sufficient kidney function had not been restored in that time to sustain nitrogen balance unaided, since although a urinary volume of 910 cc. was achieved on the last day of life, there was not adequate concentration to ensure removal of large amounts of uremic metabolites from the body. It is certain, however, that the procedure of peritoneal lavage prolonged the patient's life at least ten to fourteen days beyond the expected survival period in complete anuria. Despite the optimistic figures given by Eagle and Longcope,[17] treatment with intramuscular BAL did not appear to effect significant detoxification of the ingested mercury; since the drug could not be obtained until eight hours after the onset of poisoning, it is possible that administration at an earlier time in the illness would have been more effective.

The difficulty in maintaining free flow in peritoneal lavage in this case is best explained, in retrospect, by the supervention of sepsis and adhesions in the abdomen. It is believed that the patient's lack of co-operation in tampering with the apparatus and skin incisions had much to do with this situation; the likelihood of air-borne contamination around the outflow suction, the undecided influence of intestinal perforation and the ever-present possibility of contamination during manipulations of the apparatus, which were not carried out under operating-room asepsis, must also be borne in mind. Again, the patient's summary removal of the Miller–Abbott tube undoubtedly aided in increasing intra-abdominal pressure, which constituted another interference with free intraperitoneal flow.

On the basis of this experience it seems that peritoneal infection is a danger that, as stated by other authors, must be taken into consideration but need not be considered a barrier to institution of this therapy in cases that can be suitably controlled. On the contrary, the survival of this anuric patient for twenty-seven days is regarded as an encouraging result pointing to a better prognosis in similar cases handled with improved technic.

Summary

The literature pertaining to treatment of acute uremia by peritoneal lavage is reviewed.

A case is reported in which continuous peritoneal lavage for twelve days resulted in survival for twenty-six days after complete renal shutdown due to mercuric chloride poisoning.

The importance of avoiding peritoneal infection in this procedure is stressed, but further evidence is added for the growing opinion that "substitution" for the nonfunctioning kidneys in acute uremia is a practicable and useful procedure.

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MEDICAL PROGRESS

HEMATOLOGY*

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THIS report covers recent progress in the investigation and treatment of the anemias and the hemorrhagic diseases.

Anemias

As in previous progress reports, the anemias are classified primarily on etiologic grounds. Such a classification is simple and easily remembered and may be said to be based on economic principles: the bone-marrow "factory" requires materials for the production of its most important finished product, the red cell. Anemia results when the materials necessary for supplying the bone-marrow factories are inadequate, the factories themselves are inadequate or there is an excessive loss either by hemorrhage or by increased breakdown of the finished product, the red cell. Stated in more conventional scientific terms the anemias may be classified as due to deficiency of materials, bone-marrow disturbances and excessive blood loss, whether hemorrhagic or hemolytic.

Deficiency Anemias

Folic acid. The outstanding advance of the year is undoubtedly the advent of folic acid as a therapeutic agent in deficiency syndromes associated with macrocytosis of the red cells.

The devious routes by which folic acid came into being as a drug that the medical practitioner could use in his daily practice are fully described in a comprehensive article by Berry and Spies.[1] The apparently dull and impractical researches of bacteriologists, nutritionists, chemists and other "pure" scientists finally led to the development of a highly potent agent that, in a dosage of a few milligrams a day, was sufficient to result in remissions in pernicious anemia, sprue and related conditions.

The lowly bacterium, more particularly the *Lactobacillus casei*, provided the test subject for various growth factors, which could then be methodically studied. Snell and Peterson[2] found that these bacteria required extracts of plants or animals for proper growth. Yeast extract and certain fractions of liver extract were both rich sources of the essential growth factor, or the *L. casei* factor as it came to be called. Patient fractionation finally yielded a relatively simple material that was present in high concentration in spinach, a leafy vegetable — hence the term "folic acid." The pure compound was seventy-five to one hundred and thirty-seven thousand times as active as a standard liver fraction.

Since 1932 Wills and Bilimoria[3] had been working on a type of anemia that could be produced in monkeys by a diet similar to that consumed by

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certain Indian natives. This anemia, which was macrocytic in type, could be prevented or cured by a crude autolyzed yeast extract or by Cohn's liver extract, fraction G. The exact vitamin responsible could not be determined but was called vitamin M. When the *L. casei* factor became available, it was used in the deficient monkeys and resulted in a dramatic return to normal of all evidences of the deficiency state, including the abnormal blood picture. Other investigators, often working in large teams (fifteen authors are listed in one article), attacked the problem of certain deficiency states in chicks in which a macrocytic hyperchromic anemia was present.[4] Prevention and cure of this deficiency was finally achieved by a fraction of the vitamin B complex. The exact nature of this material, which was called the vitamin B_c factor (vitamin B_c, chick factor) could not at first be determined, but work by other groups demonstrated that effects identical with those induced by the vitamin B_c factor could be duplicated by the use of the *L. casei* factor. Conversely, the vitamin B_c factor replaced the *L. casei* growth factor in experimental work with *L. casei*. Synthesis of the material, which was called pteroylglutamic acid, was finally achieved by a group of chemists working in the Lederle Laboratories,[4] and it was then determined that this new compound was equally effective in the deficiency anemia of chicks, the M deficiency state of monkeys and the *L. casei* nutritional deficiency of bacteria.

The folic acid material, which was extracted from previously discarded liver-extract residues, was chemically analyzed and later synthesized and was then supplied to a number of investigators interested in nutritional problems. Among these was Spies,[5] whose investigations in pellagra and in other deficiencies involving the vitamin B complex had been outstanding. Spies and his collaborators had previously tried, with relatively little success, fractions of the vitamin B complex in certain cases of anemia, which were usually of the macrocytic type. With the use of the newly synthesized folic acid striking clinical and hematologic effects were obtained.[6–11] The hematologic response, which was considered to be identical with that found in pernicious anemia when liver extract was given, showed a reticulocytosis with a subsequent rise in red cells, hemoglobin and leukocytes. These results were quickly confirmed by various observers, including Moore and his associates,[12] who reported clinical and hematologic remissions in 2 patients with pernicious anemia after the daily oral administration for ten days of 30 mg. and 100 mg., respectively, of the synthetic material. A patient with the macrocytic anemia of nontropical sprue and another with pernicious anemia of pregnancy responded similarly when given the material intravenously in a dosage of 20 mg. Zuelzer and Ogden[13] showed that folic acid was also effective in the treatment of the megaloblastic anemia of infancy. These cases, which presented pallor, vomiting, fever, slight cardiac enlargement and, at times, splenomegaly, demonstrated a normochromic, macrocytic blood picture and a megaloblastic bone marrow. Folic acid resulted in reticulocytosis, erythrocytosis and a return of the bone marrow to normal.

Numerous reports have since appeared from various parts of the country and have shown conclusively that 5 to 20 mg. of folic acid given orally as a daily dose is sufficient to induce a well marked, often maximal, reticulocytosis and a well defined, if not maximal, erythrocytosis. Simultaneously, striking responses take place clinically. It is not yet completely settled whether folic acid causes consistently maximal responses in erythrocytes similar to these produced by liver extract, or whether folic acid alone prevents or improves the neurologic lesions of pernicious anemia. More theoretical questions are discussed below. Watson and Castle[14] demonstrated the effectiveness of a material other than pure liver in certain cases of "nutritional macrocytic anemia," especially in pregnancy. These cases had failed to respond to the parenteral administration of refined liver extract in doses ordinarily sufficient to induce a remission in ordinary cases of pernicious anemia, but when a crude oral extract of liver (Valentine) was given, excellent responses occurred. Unfortunately, sufficiently large doses of folic acid were not given to these patients to determine whether they would have responded to this medication. The observations are nevertheless of great importance as indicative of the fact that nutritional macrocytic anemias may be of various types: some responding to pure liver extract, some responding to folic acid but not to pure liver extract, and some responding to either material (and perhaps some responding to neither).

Spies and his co-workers demonstrated that folic acid was effective in all the deficiency states associated with a macrocytic anemia. These included not only pernicious anemia but also certain cases of vitamin B complex deficiency. Sprue seemed to be a condition in which this material could well be effective. The favorable response of a few cases of nontropical sprue to folic acid had already been noted by Moore et al.[12] and by Darby and Jones.[15] In Cuba, Spies and his associates[9, 10] quickly collected a group of cases of tropical sprue treated with folic acid. Preliminary observations by Spies and his co-workers[9] and later by Spies and Suarez[16] in Puerto Rico demonstrated that small doses of material (5 to 15 mg. daily by mouth) usually resulted in dramatic clinical and hematologic improvement; this was often far greater than that obtained by the use of large doses of crude liver extract in association with a well balanced diet.

The synthesis of folic acid was a difficult chemical task and was undertaken by a large group of

chemists working in the Lederle Laboratories. Although synthesis was first announced in 1945, the actual details of chemical identification and methods were kept secret until approximately a year later, when a publication by Angier and his collaborators[4] appeared. Chemically, folic acid consists of a substituted pteridine combined with a molecule of para-aminobenzoic acid and a molecule of glutamic acid to which the name "pteroylglutamic acid" was applied.

The theoretical aspects of folic acid therapy resulted in a whole new set of problems to plague the investigator especially at a time when it seemed that the problem of pernicious anemia was to a great extent solved or at least quiescent. The response to two entirely different substances is puzzling. Castle's theory of the interaction of an "extrinsic" factor in the food with an "intrinsic factor" in the gastric juice leading to the development of a "liver-extract factor" or an "erythrocyte-maturation factor" is by no means invalidated. Folic acid appears to be neither the extrinsic nor the intrinsic factor. Heinle[17] discusses these theoretical matters at length. On the basis of preliminary experimental data, he concludes that a "principle of liver extract, possibly the antipernicious anemia factor is concerned with the release of free folic acid from conjugates of the vitamin." This would, of course, explain the identical action of two distinctly different substances; patients with pernicious anemia, although they might possess adequate amounts of conjugated folic acid would find it of little value because free folic acid could not be liberated. Liver extract apparently releases this material from the conjugated substance, and folic acid, of course, supplies it ready made. In a review of the clinical and experimental aspects of folic acid, Doan[18, 19] makes the point that this material is essential for normal cellular metabolism; lacking it, the marrow becomes defective with resulting pernicious anemia. Perhaps to confuse the picture even more for the ordinary reader is the report by Spies and his co-workers[20, 21] on the antianemic properties of thymine. This material, which is derived from thymonucleic acid, was also effective (in massive doses of 4.5 to 15 gm. daily) in causing remissions in pernicious anemia. The relation of this material to folic acid is quite obscure, although Spies and his collaborators suggest that the latter substance acts as an enzyme or coenzyme in the synthesis of thymine or a thymine-like material.

Other aspects of pernicious anemia. The following papers deal with didactic matters that, in comparison with the dramatic events relating to folic acid therapy, seem relatively dull. Schwartz and Rappolt[22] report 3 cases of pernicious anemia in Chinese hospitalized at the Cook County Hospital. Another case in a Chinese is reported by Hartwell[23] from Honolulu. The occurrence of carcinoma of the esophagus in a long-established case of pernicious anemia is described by Cooke,[24] and that of leiomyosarcoma of the stomach by Schindler and his associates.[25] Typical examples of the disease occurring in children are described by Jonssen[26] and by Peterson and Dunn,[27] as well as by Zuelzer and Ogden.[13] The following criteria should be present: macrocytic anemia, histamine-resistant achlorhydria, megaloblastic marrow, reticulocytosis after liver-extract therapy and necessity for continued administration of liver extract. The occurrence of pernicious anemia in association with intestinal strictures and anastomosis is discussed by Richardson,[28] who believes that a stagnant intestinal loop, by causing damage to the intestinal mucosa, helps to bring about the disease. A likelier explanation is that malabsorption of the liver-extract factor results in a conditioned deficiency of this substance.

Cayer, Ruffin and Perlzweig[29–31] studied the levels of various vitamins in the disease. Those of vitamin A and pyridoxin were within normal limits in all patients, but those of niacin (nicotinic acid), riboflavin and thiamine were below normal. The authors concluded that, if liver extract alone does not result in a completely adequate response in pernicious anemia, components of the vitamin B complex should be given. (This is even more applicable to folic acid, a fraction of the vitamin B complex.)

Liver-extract sensitivity not infrequently develops in the course of parenteral therapy. In a large series of cases treated at the Cook County Hospital in Chicago, Schwartz and Legere[32] found that 17 per cent of patients developed manifestations of sensitivity including itching, flushing, tachycardia, asthmatic reaction or even shock. Treatment of this sensitivity is relatively easy in most cases and consists in a change of the brand of extract, particularly to one in which beef liver is used instead of the pork product, reduction of the dose of material and desensitization, which is often unsatisfactory. In stubborn cases Schwartz suggests the use of a histamine protein complex to produce antihistamine antibodies; with the use of this "anti-H" material* good results were obtained in 10 of 11 cases. Folic acid has naturally revolutionized the treatment of desensitization.

The neurologic complications of pernicious anemia are in some ways far more important than the hematologic — and far less readily controlled. Although disorders due to disturbances of the posterolateral column of the spinal cord are best known, Rundles[33] points out that three other types of involvement may occur: cerebral, olfactory and that of the peripheral nerves and nerve roots. Olfactory symptoms were found in 4 of 20 cases; perversion or loss of taste for foods, especially for proteins, occurred independently of atrophic or inflammatory changes of the lingual mucosa. Eleven of the 20 patients had involvement of the peripheral nerves

*Obtainable from Parke, Davis and Company, of Detroit.

as well as of the posterior columns of the spinal cord. Foster[34] also points out the importance of peripheral-nerve involvement in pernicious anemia. Although it is clinically difficult to distinguish involvement of the posterior column from that of the peripheral nerve, it is essential to give maximum therapy, since peripheral nerves have a marked regenerative capacity and may thus be influenced by treatment.

Large doses of liver extract are recommended to combat the neurologic disorder, 30 to 60 units of concentrated extract being given weekly by parenteral injection until a maximum neurologic response has been obtained. Although the degree of remission cannot be foretold, one can be certain that with the continued use of about 15 units of extract every ten to fourteen days, no neurologic relapse will occur.

Iron-deficiency anemia. Schwartz and Flowers[35] describe the changes in the blood that occur in the course of gradually developing chronic iron deficiency, usually owing to chronic bleeding. There is a linear fall in the hemoglobin, with the red-cell count constantly lagging behind and resulting in an ever-decreasing color index. As this diminishes, characteristic changes in the red cells develop: microcytosis, hypochromia, anisocytosis and poikilocytosis. Recognition of the iron-deficiency state is important, since liver extract is of no value. Although therapy with iron salts may be effective, a search for an etiologic factor must be made. Goetsch, Moore and Minnich[36] describe the effects of massive doses of iron intravenously in patients with hypochromic anemia. Although the reticulocyte response is often higher and the average rate of hemoglobin regeneration greater than with oral therapy, toxic reactions are frequent and severe and thus militate against the use of this therapy in clinical practice.

The use of molybedenum in combination with iron in the treatment of iron deficiency is described by Neary[37] and Healy.[38] Molybedenum, a so-called "trace element," was first used in the milk-induced anemia of rats. Neary studied 22 patients with iron deficiency of pregnancy, of whom half received ferrous sulfate alone, and half molybedenum ferrous sulfate. The patients receiving the latter combination showed a more rapid therapeutic response. Healy stated that the response to molybedenum was striking, with an average daily increase in hemoglobin of 0.36 gm. per 100 cc., whereas with iron alone, in comparable cases, the average increment was only 0.12 gm. per 100 cc. The results in both these papers are subject to further critical evaluation.

Schulze and Morgan[39] found that the addition of ascorbic acid to iron was valueless in the therapy of iron-deficiency anemia of children. It may be added parenthetically that in the presence of a state of iron deficiency, iron alone is usually all that is required for therapy. It is highly questionable whether liver extract, folic acid, copper, molybedenum and vitamins of various types do anything except add to the cost of the preparation. Another more serious danger in the treatment of iron deficiency results from the treatment of the anemia as such, rather than finding out, first of all, what the underlying cause may be. I have seen a number of cases of hypochromic anemia in which prolonged therapy (usually with liver extract) was given but in which examination of the stools later demonstrated strong reactions for occult blood and x-ray films of the gastrointestinal tract demonstrated a bleeding lesion, usually cancer. In every case of hypochromic anemia of obscure etiology, it is *imperative* to search for a bleeding lesion. Diaphragmatic hernia is occasionally found, as pointed out by Chevallier and Danel.[40] These authors, however, suggest that the anemia is due to an inflammatory disturbance of the gastric mucosa. In the cases that I have observed, occult blood has always been demonstrated, provided enough stools were examined. In some cases brisk or constant bleeding is present.

Bone-Marrow Anemias

Bone-marrow disturbances are usually associated with a pancytopenia — that is, reduction in red cells, white cells (granulocytes) and platelets. They are brought about by diminished growth in the marrow (hypoplasia or aplasia), by foreign-tissue infiltration or proliferation (leukemia, neoplasm or sclerosis) or by splenic inhibition in certain conditions, usually splenomegaly.

Aplastic and hypoplastic anemia. Quinacrine (Atabrine) as a possible cause of various types of bone-marrow disturbances was suspected during the war, but for obvious reasons such suspicions were not publicized. Custer[41] reports 57 cases of aplastic anemia in soldiers from the Pacific and the China and India-Burma theaters. Although the Army personnel in these areas was only one twenty-fifth to one seventh of the total troop strength, two and a half times as many cases of aplastic anemia appeared as in soldiers from the European Theater. Quinacrine was used by a large portion of the personnel in the Pacific and the China and India-Burma theaters, and, in addition to anemia, dermatitis, weakness and hemorrhagic disturbances were noted. Most and Hayman[42] report a single case of quinacrine aplastic anemia. A report by Greenfield[43] on aplastic anemia that was thought to be due to a "rifle-bore cleaner" is of interest in that quinacrine had also been used by the patient.

New medications containing the benzene ring suggest new causes for aplasia or hypoplasia of the bone marrow. Tridione, which was recently introduced as an anticonvulsant drug, has been implicated in cases reported by Harrison, Johnson and Ayer[44] and by Mackay and Gottstein.[45] Other chemical agents recently implicated in the production of aplastic anemia include the sulfonamides (Denny and Menten[46]), trinitrotoluol (Sievers,

Stump and Monaco[47, 48]), Stovarsol (Schrire[49]), calcium bisulfite (Carlson[50]), estradiol benzoate — estrogen (Chevallier and Umdenstock[51]) and benzene (Aubert[52]). Although some of the reports are not convincing regarding a direct relation of the chemical to the aplasia, it is important to record even possibilities, since this is a chemical age and potentially dangerous materials must be guarded against. It should also be pointed out that some cases of aplastic anemia, particularly in children, are probably largely congenital in origin and become definitely evident only after a drug such as sulfadiazine has been given. The Nagasaki and Hiroshima atomic bomb explosions led to countless cases of radiation sickness. Death followed in most cases, but patients who were relatively slightly affected developed varying degrees of bone-marrow involvement. One of the first articles on this subject dealing principally with the clinical effects noted is that of Timmes.[53] Pancytopenia was present in most cases but in others "selective" cytopenias were present, including extreme granulocytopenia, thrombocytopenia and anemia. Lack of facilities made therapy difficult; thus, only rare cases received transfusions of blood and penicillin. Hemorrhage from lack of platelets and uncontrolled infection from agranulocytosis were frequently observed. In the mildest cases the patients recovered. It will be of interest for future investigation to note whether leukemia or other leukocytic proliferations occur in greater incidence in persons exposed to the atomic bomb than in other groups. The therapy of aplastic anemia is extremely difficult and often of no avail. Folic acid has been used by Denny and Menten[46] and by Peat[54] with questionable results. I have seen favorable results from splenectomy in the congenital hypoplastic anemia of children, and this procedure should be seriously considered, particularly if megakaryocytes are not completely lacking. Splenectomy apparently removes a normal inhibitory or regulatory influence on the bone marrow and thus allows more marked red-cell, white-cell and platelet production to take place than would otherwise occur.

Anemias Associated with Increased Blood Destruction

The anemias of increased blood loss may be either hemorrhagic or hemolytic. The former are of chief importance from the standpoint of diagnosis, particularly in the presence of continued slight bleeding from the gastrointestinal tract. The latter anemias are assuming an ever-increasing significance as more and more cases are being recognized. They may be classified as follows: the familial and hereditary, including the spherocytic, target-oval (Mediterranean) and target-sickle (sickle-cell) types; the acquired, comprising the acute, subacute and chronic, those caused by infections, chemicals, toxins and parasites (of known etiology), those associated with leukemia, lymphoma, Hodgkin's disease and so forth (symptomatic), those associated with isoantibodies, such as hemolysins and agglutinins and the hypersplenic type; and the hemoglobinurias.

Familial types. The familial and hereditary hemolytic anemias are for the most part readily differentiated according to the predominating type of red-cell picture. The spherocytic type is the best known and is associated with the presence of small, thick dense-appearing red cells, which have an increased fragility in solutions of hypotonic sodium chloride. Several investigators have shown that the red cells of this disease have a diminished life span in a normal circulation; when the spleen is removed, the life span of the spherocyte is normal. The cause of the spherocytosis is unknown. Most authorities consider that the spherocyte is produced by an abnormally functioning marrow. This reasoning is confirmed by two findings: blood introduced into the circulation in a case of familial spherocytosis survives at a normal rate — that is, there is no vascular hemolytic factor; and tests of the red cells with an antiglobulin serum (Boorman, Dodd and Loutit[55]) fail to show the presence of adsorbed antibody. Dameshek and Schwartz,[56] on the other hand, contend that since spherocytosis can be experimentally produced and since this abnormality indicates a red cell in the process of hemolytic destruction, a hemolytic substance is somewhere present, whether demonstrable or not. They cite other evidence. It is also possible that hemolysin or agglutinin is specific for the patient's own cells and thus does not cause increased destruction of introduced red cells. These hypotheses are being studied. The hemolytic crisis, which is associated with greatly increased spherocytosis and which may develop at any time in the course of the disease, may indicate an extrinsic factor or an accentuation of the already existing cause of the spherocytosis. Familial crises are reported by Horne et al.[57] and have previously been observed by Dedichen[58] and Dameshek.[59] In the cases presented by Horne and his associates the red cells contained peculiar inclusion bodies that were perhaps related to Howell-Jolly bodies.

The various clinical types of the target-cell and oval-cell syndromes, which occur primarily in persons of Mediterranean ancestry, have been reported by Dameshek.[60] All cases show target, oval and stippled cells and increased hypotonic resistance of the red cells. A typical mild case with hypochromic erythrocytosis occurring in a Chinese is reported by Greenblatt, Cohn and Deutsch.[61] Stiles, Manlove and Dangerfield[62] presented a characteristic case in a Negro in whom there was complete absence of sickling. Another probable case in a Negro is reported by Faber and Roth.[63] Two cases occurred in Palestine in Bucharan Jews whose ancestors had lived for perhaps a thousand years on the shores of the Caspian Sea.[64] Another case is reported from

South Africa in a European of German and French origin.[65]

The mild cases of Mediterranean syndrome have no great significance, except that they represent carriers of a trait that is transmitted in a Mendelian-dominant fashion. Two affected carriers may beget children with the fatal Cooley's anemia, the severest form of this disease. Mild and moderately severe cases are often mistaken for iron-deficiency anemia, lead poisoning, spherocytic hemolytic anemia and even polycythemia. No satisfactory therapy has as yet been established.

Sickle-cell disease, which is largely present in people of African stock, may occur in persons of Mediterranean origin. Sickle-cell anemia with ankle ulcers is reported in a white brother and sister.[66] The sickle-cell trait is noted on the average in 7 to 8 per cent of Negroes. In 5500 West Africans, Findlay, Robertson and Zacharias[67] found an incidence of 12.5 per cent sickling. Of 403 South African Bantus, however, Altmann[68, 69] observed only 0.25 per cent with sickling. In the United States Army, Henderson and Thornell[70] reported a 7 per cent incidence of the trait. It is of interest that, under conditions of lowered arterial oxygen tension, none of the patients showed intravascular sickling or increased hemolysis.

Ponder[71] studied the highly interesting question of how and why the red cell sickles under conditions of reduced oxygen tension, and his paper should be read in the original by those who are interested. The pathogenesis of the development of thrombotic manifestations in sickle-cell anemia is discussed by Murphy and Shapiro.[72] The red cells, under conditions of anoxemia, become rigid, producing mechanical impaction and eventually resulting in slowing of blood flow and thrombosis. The cardiovascular lesions of sickle-cell disease are described by Wintrobe.[73] Two cases — one of them fatal — of sickle-cell anemia complicated by pregnancy are reported by Noyes[74] and by Zimring.[75] In the latter case, there was acute illness, pallor and jaundice during labor.

Two new familial hemolytic syndromes have been described in the past year. Rundles and Falls[76] report a hypochromic, microcytic anemia occurring in association with splenomegaly, increased hypotonic resistance of the red cells and failure to respond to splenectomy. Although in many respects the cases resemble those with Mediterranean anemia, no evidence of Mediterranean ancestry was present. Stransky and Regala[77] describe 4 cases of hemolytic anemia in 5 Filipino siblings. There was no spherocytosis or leptocytosis, but many nucleated red cells were present. Splenectomy was without effect in 3 cases.

Acquired types. Ross and Paegel[78] present the case of a four-year-old child who developed an extremely severe acute hemolytic anemia with hemoglobinuria after the administration of a small amount of sulfadiazine. Hypersensitivity to this drug had probably occurred as the result of two previous administrations. Improvement did not occur until a vein was cannulated and large amounts of blood (1100 cc.) given over a period of eight hours. Cockett[79] describes the case of a young man who received benzyl-sulfanilamide as a prophylaxis for minor second-degree burns of the legs. Three days later, after 17 gm. had been given, weakness, loin pains, hematuria and severe hemolytic anemia developed. Recovery ensued after the administration of two transfusions of blood. Young, Valentine and Howland[80] report the first case of acute hemolysis following the injection of neoarsphenamine. A previous injection of the drug had caused nausea and vomiting. Five minutes after the second injection the patient developed severe symptoms and died within twenty-four hours. Autopsy showed hemoglobinuria, icterus, spherocytosis and normoblastosis.

Jope[81] studied the disappearance of sulfmethemoglobin in 7 cyanotic trinitrothrene workers who had developed sulfhemoglobinemia. The abnormal hemoglobin compound was retained within the affected red cell until its destruction, which occurred on the average in one hundred and sixteen days. This period may be considered the life span of the red cell containing sulfhemoglobin.

The development of isoantibodies (hemolysins or agglutinins) within the body may result in autohemolysis and thus in hemolytic anemia. Finland et al.[82] found hemolytic anemia in 11 of 200 cases of primary atypical pneumonia. This usually occurred when the maximal titers of cold hemagglutinin were present and was apparently independent of sulfonamide therapy. With marked cold autoagglutination, there was usually a wide thermal range, so that hemolysis could occur within the circulation as the result of agglutination, which results in increased mechanical fragility. A more general article on the clinical significance of cold hemagglutinins is that of Young.[83] Lubinski and Goldbloom[84] report a fatal case of hemolytic anemia in which the cold hemagglutinin had a wide thermal amplitude and was active to some extent at incubator temperature. Boorman and his associates[85] consider some of the mechanisms by which cold hemagglutinins may become activated to produce hemolysis in the circulation even at 37°C. Cases showing abnormal isoantibodies, either agglutinins or hemolysins, require special consideration when transfusions are contemplated. As stated above antibodies are adsorbed to the red cells in some cases and are not found in the serum. Boorman, Dodd and Loutit[55] demonstrated adsorbed agglutinin in a series of cases of idiopathic acquired hemolytic anemia by testing the red cells with antihuman globulin rabbit serum. Adsorbed antibody was not demonstrated in familial spherocytosis.

Transfusions and splenectomy remain the chief therapeutic agents in hemolytic anemia. Transfusions alone are rarely effective except in cases due to chemical poisoning and in those due to parasites (malaria and Oroya fever). Splenectomy must be resorted to in many cases, particularly when transfusions have been ineffectual. An excellent prognosis can be promised in familial spherocytosis, but in the acquired hemolytic cases, the outlook is not entirely certain. About 7 of 10 patients do well after splenectomy, but the others are either partially or only slightly benefited, if at all. Attempts to diminish red-cell destruction by a diet low in fat have proved ineffective (Evans[86]). Rare patients with refractory hemolytic anemia have recovered after the removal of an ovarian tumor (Singer and Dameshek[87] and Jones and Tillman[88]). Penicillin therapy was used with a favorable effect by Merino[89] in a case of human bartonellosis.

Anemia of Infection

Infection causes disturbances in red-cell development in the bone marrow. Such cases have been studied extensively in Wintrobe's laboratory and reported on in a series of articles by Cartwright and his collaborators.[90] It was found that a reduction in serum iron, an increase in serum copper, an increase in erythrocyte protoporphyrin and an increase in coproporphyrin output in the urine were present. The serum bilirubin and urobilinogen excretion were normal and thus indicated that hemolysis was not a factor. The red cells were normocytic and normochromic. The anemia failed to respond to iron (oral or intravenous), copper, components of the vitamin B complex, ascorbic acid, Amigen, globin, cystin, methionine or crude liver therapy. Indications of an altered iron metabolism were present, the iron being diverted from the marrow to the tissues and thus being made unavailable for hemoglobin synthesis.

(To be concluded)

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NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-SIXTH ANNIVERSARY

House of Delegates, June 18, 19 and 20, 1947

THE House of Delegates convened at the Wentworth Hotel, Newcastle, on June 18, 1947, at 7:30 p.m., with Speaker Leslie K. Sycamore presiding.

The following members answered the roll call:

The President, *ex-officio*
The Vice-President, *ex-officio*
The Secretary-Treasurer, *ex-officio*
Samuel Feiner, Ashland
Nathan Brody, Laconia
W. J. Paul Dye, Wolfeboro
Francis J. C. Dube, Center Ossipee
Albert C. Johnston, Keene
James N. Ballou, Keene
Marjorie B. Parsons, Colebrook
Joseph E. LaRochelle, Gorham (alternate for Francis M. Appleton)
Israel A. Dinerman, Canaan
Leslie K. Sycamore, Hanover
Leslie E. McKinlay, North Haverhill
Clarence E. Dunbar, Manchester
Daniel J. Sullivan, Nashua
Samuel Fraser, New Boston
Loren F. Richards, Nashua
Robert R. Rix, Manchester
Philip M. L. Forsberg, Concord
Andrew L. MacMillan, Concord
Francis Brown, Henniker
John W. Blaisdell, Epping
Donald W. Leonard, Exeter
Fred Fernald, Nottingham
Raymond R. Perreault, Rochester
Daniel F. McCooey, Dover
Donald C. Moriarty, Newport
B. Read Lewin, Claremont
George C. Wilkins, Manchester
Samuel T. Ladd, Portsmouth
Deering G. Smith, Nashua

The Speaker declared a quorum present, and appointed the Credentials Committee as follows: Drs. Johnston, Moriarty and Dube.

On motion duly made and seconded, it was voted to omit the reading of the previous minutes, because of the publication of the proceedings.

On motion duly made and seconded, it was voted to dispense with the reading of the reports of the councilors, since they will be published in the *Transactions*.

To the Committee on Officers' Reports, the Speaker appointed Andrew L. MacMillan, of Concord (chairman), and Loren F. Richards, of Nashua, and Donald W. Leonard, of Exeter. To the Committee on Memorials, he appointed Raymond R. Perreault, of Rochester, Clarence E. Dunbar, of Manchester, and B. Read Lewin, of Claremont. To the Committee on Nominations, he appointed W. J. Paul Dye, of Wolfeboro (chairman), Samuel Feiner, of Ashland, Joseph E. LaRochelle and Robert R. Rix, of Manchester, and Israel A. Dinerman, of Canaan.

The Secretary-Treasurer, Dr. Carleton R. Metcalf, presented his report, as follows:

The total membership on December 31, 1945, was 528; that on December 31, 1946, was as follows:

PAID		
Belknap County	32	
Carroll County	16	
Cheshire County	33	
Coos County	33	
Grafton County	69	
Hillsborough County	159	
Merrimack County	77	
Rockingham County	55	
Strafford County	39	
Sullivan County	18	
State members	3	
	—	534
UNPAID		
Life members	18	
Honorary members	5	
	—	23
		557

FINANCIAL STATEMENT

RECEIPTS

January 1, 1946 — balance forward	$107.24
Belknap County	168.00
Carroll County	90.00
Cheshire County	256.00
Coos County	162.00
Grafton County	352.00
Hillsborough County	852.00
Merrimack County	442.00
Rockingham County	318.00
Sullivan County	118.00
Strafford County	217.00
Cash received at annual meeting	73.00
Checks received at annual meeting	14.00
Members not in county society	18.00
Donations to National Physicians Committee (Strafford County, $34; Belknap County, $28; Hillsborough County, $123; Merrimack County, $50.00)	235.00
Benevolence Fund (Rockingham County Auxiliary, $40; Strafford County Auxiliary 1945–46, $20; Merrimack County Auxiliary, $20)	80.00
General Fund — Trustees	500.00
Receipts, 1945 annual meeting	85.08
	$4087.32

EXPENDITURES

New England Journal of Medicine:	
Journals	$515.49
Tabular material	3.10
Carleton R. Metcalf (salary)	500.00
Printing	164.71
Envelopes and stamps	56.00
Halftone cuts	55.54
Clerical work	155.50
Telephone and telegraph calls	33.99
Retaining fee	100.00
Guest speakers (dinner)	85.04
Cancer Committee	60.00
Dues collected at annual meeting	80.00
Benevolence Fund:	
Rockingham County	40.00
Strafford County	20.00
Merrimack County	20.00
National Physicians Committee (donations):	
Strafford County	34.00
Belknap County	28.00
Hillsborough County	123.00
Merrimack County	50.00
Madeline A. May (stenographer at annual meeting)	301.19
Committee luncheons	162.45
New England Medical Council	200.00
Deering G. Smith (expenses as delegate to American Medical Association, 1945–46)	691.89
Deering G. Smith, Committee in Medical Preparedness	152.93
Auditor, trustees books	10.00
Refund on dues	12.00
Service charges at bank	2.39
	$3657.22
Balance, January 1, 1947	430.10
	$4087.32

Although no money was added to the Benevolence Fund from the annual dues during 1946, donations totaling $80 were received from the auxiliaries of Rockingham County, Strafford County and Merrimack County.

In accordance with instructions from the House of Delegates $60 was given to the Cancer Committee. The number of members on this committee was increased to five.

The Committee on Mental Hygiene was asked to formulate a definite program for outpatient psychiatric care and to report at this meeting.

A year ago a National Emergency Committee was formed consisting of five men who served in the recent war. This committee was asked to consider the service of doctors in the war with the thought that in a future emergency a more efficient plan for medical care could be invoked.

The New Hampshire Board of Health has asked us to form a Committee on Industrial Health, and the Committee on Rural Medical Service of the American Medical Association has asked us to form a Committee on Rural Medical Service. Both suggestions have been referred to the speaker of the House of Delegates.

The sum of $100 was provided for our share in the Council of the New England State Medical Societies. The several meetings of this council were beneficial to New Hampshire, and it is recommended that $100 be donated to the Council so that we may maintain our membership.

All members of the Society were notified that they could have all issues of the *New England Journal of Medicine* by sending $1.50 a year directly to the *Journal*, and all county societies were notified of the amendment to the By-laws that changed the phrase "affiliate member" to "life member."

The Board of Health was informed that in the opinion of the House of Delegates health conditions in restaurants and hotels are lax and should be corrected. This alleged laxity is apparently due to an appropriation from the General Court that does not permit the employment of sufficient inspectors.

The New Hampshire Hospital Association was advised that, in the opinion of the House of Delegates, routine chest x-ray examination of patients entering New Hampshire hospitals was a worthy procedure.

The New Hampshire Board of Welfare was requested to send a copy of the present fee table to every member of the Society and was informed that the fee allowances of the Blue Shield would be appropriate for indigent patients who are under the supervision of the Welfare Department.

The annual dues of the Society were raised to $10.00.

A special meeting of the House of Delegates was held last October at the Snow Shoe Club in Concord to consider the hometown care of veterans with service-connected disabilities. This meeting was attended by a representative of the Veterans Administration from Boston, Dr. Cooper, as well as by Dr. Drury, of the Manchester office. The decision was left in the hands of a special committee, with power to act. This special committee had several meetings, drew up an agreement and prepared a fee table for the care of veterans. The agreement has been accepted by the Veterans Administration. The fee table was rejected, in part, by the Administration on the ground that some of the fees were larger than those charged other patients for similar services in New Hampshire communities. The Veterans' Administration countered with a fee table that represented the maximum amounts that the Government was willing to pay. Copies of this fee table and of the agreement were sent to each county society with the request that it consider the matter and instruct its delegates in the proper action to be taken at this meeting.

The Taft Bill (S. 545) will probably have hearings in the Senate soon, and according to the newspapers, a revised version of the Wagner–Murray–Dingell Bill is also to be presented.

The most important legislation that came before the General Court this year was the hearing on the elimination of Bang's disease in cattle. The Society was represented by the Committee on Public Relations. Dr. Blood spoke in favor of a continuation of the program, and the Secretary gave a vivid description of undulant fever, with which he was afflicted in 1941.

Our attorney, Mr. Sulloway, was given his usual retaining fee of $100. It should be remembered that any member of the Society is privileged to confer, without expense, with Mr. Sulloway on any legal difficulty pertaining to the practice of medicine.

According to the by-laws of the American Medical Association the delegate from this state, as well as the alternate delegate, should be elected for two years rather than for one year. It should also be noted that both the delegate and the alternate delegate must have been fellows of the American Medical Association for a period of two years before they are elected.

A return postal card was sent to all members during the course of the year asking them to signify if they would like to serve on one of the committees of the Society. The names of those who wish to serve on a committee have been given to the Committee on Nominations.

A second postal card was sent soliciting volunteers for a speakers' bureau. A questionnaire was sent to all members requesting suggestions to make the work of the Society more interesting and more beneficial.

The Missouri State Medical Association sponsored a contest last year among school children, who were asked to write a brief essay on the subject, "What Can Our Community Do to Improve Its Health?" Suitable prizes were awarded. It might be worth while to have such a contest in New Hampshire next fall. We might find some "sore spots" that could be corrected in a constructive way. If such a contest meets with your approval, I suggest the expenditure of $200 to $300 in prizes.

For the present, it seems that we must hold our annual meeting at some summer hotel in June. Now that we have returned to a two-day meeting it may be considered unwise to hold a meeting in Manchester because it is practically impossible in that city to get adequate hotel accommodations.

On motion duly made and seconded, it was voted that the report of the Secretary-Treasurer be referred to the Committee on Officers' Reports.

Dr. Macmillan, chairman of the Committee on Officers' Reports, then stated that the Committee had approved the Secretary's report.

The speaker then suggested that Dr. Metcalf say a little more regarding the question of sponsoring a contest among school children on community Health.

Dr. Metcalf replied that the contest in Missouri apparently received a considerable response from the school children, that it gave the children and the people of Missouri the idea that physicians were trying to do something constructive for the betterment of health in the different communities and that, in the event that they picked up what he called a "sore spot," an attempt was made to correct that condition. The question was whether it would be worth while to try it in New Hampshire this fall.

Dr. Macmillan stated that the Committee on Officers' Reports had read Dr. Metcalf's report and approved all his suggestions.

Dr. Dye inquired whether funds were available for such a purpose.

The Secretary replied in the affirmative.

Dr. Dye moved that the Society sponsor such a contest, instructing Dr. Metcalf to proceed with it, and that the maximum expenditure be $300.

This motion was duly seconded and carried.

Dr. Dye moved that the appropriation of $100 for the expenses of the New England Medical Council be made.

The speaker asked if all the members knew what the New England Council was. He defined it as an organization of delegates from the six New England state societies to discuss the questions that concern the general region of New England. He said that it had no particular power of action but had power of recommendation to the societies, adding that it had conducted general discussions for the memberships of the societies, besides its own discussions, concerning the state of medicine in the New England area.

The President stated that he had attended all the meetings of the Council, which had been important in bringing the viewpoints of the different New England states together. He believed that the medical societies of the six New England states are today much more in accord than they have ever been before, because of the Council.

The Speaker then requested all those in favor of appropriating $100 for the expenses of the New England Medical Council to manifest assent by saying "aye."

There was a chorus of "ayes," and the motion was carried.

The report of the Committee on the Control of Cancer was then presented by the chairman, Dr. George C. Wilkins:

As usual during the past year your committee sent to every member of the society three one-page letters on important subjects pertaining to cancer diagnosis or treatment. One on cancer of the urinary tract mentioned the two most important symptoms: hematuria and a mass in the flank. Any patient presenting either of these symptoms should be cystoscoped without delay, that an early diagnosis may be made. Cancer of the digestive tract was too large a subject to be treated in one letter, but several important points were emphasized that should lead to earlier diagnosis, such as early x-ray examinations in patients with indefinite but persistent digestive disturbances and repeat x-ray examinations when the diagnosis has been indefinite. Every tumor of the digestive tract should be considered a carcinoma until proved otherwise. More careful histories and more thorough examinations will reveal carcinoma of the colon earlier. This type of carcinoma is appearing more frequently in our cancer clinics and hospitals. Our last letter contained many unrelated hints in short sentences that might refresh the memories of physicians in the methods of making correct diagnoses of cancer and in advising adequate treatment.

The New Hampshire Medical Society was the first to send cancer information of this type to its members. Now many states are doing it, some by means of comparatively voluminous pamphlets and bulletins, but your committee still prefers short, readable articles, which we hope will stimulate interest. Complete information on any phase of cancer is available in medical magazines and in books.

On May 6 the second annual Cancer Instruction Day was held in Manchester. There were eleven speakers on different phases of cancer. All talks were short and concise. A luncheon was served at noon, and the members of the Society attending the meeting are indebted to the New Hampshire Field Army of the American Cancer Society for bearing all the expenses of the meeting as part of their educational campaign. Although ninety members had indicated their intention of attending this meeting, we were again disappointed at the small number of general practitioners attending.

The Field Army has also continued its generous offer of financial assistance to any physician connected with any of the state cancer clinics to take refresher courses at a cancer center. Two physicians have taken advantage of this offer during the past year.

The lay and high-school educational projects of the Field Army have been continuously functioning, but there are still high schools that have not accepted the ideas or the pamphlets furnished by the Field Army.

The functions of the fourteen cancer clinics of the New Hampshire Cancer Commission have continued as usual. During the year ending July 1, 1946, the smallest number of new cases for several years was recorded. The number always fluctuates with economic conditions, and during the past six months more patients have appeared at the clinics and there have been more applications for financial assistance. Since 1931, when the Commission was established, these changes have been an early and significant barometer of economic changes.

The need for continued intensive education among the laity in the early signs of cancer is being constantly demonstrated by the appearance of patients with advanced cancer in doctor's offices, hospitals and clinics. We must also recognize and admit that there is a continued need for education in early recognition of cancer among the members of the medical profession. This is our problem, and we should do all in our power to remedy this situation.

Your committee expended $55.56 of the $60.00 appropriation and requests the sum of $60.00 for next year's expenses.

GEO. C. WILKINS, *Chairman*
RALPH E. MILLER
WALTER H. LACEY
ALBERT OPPENHEIMER
GEORGE F. DWINELL

Dr. Macmillan stated that the Committee on Officers' Reports had approved the report of the Committee on the Control of Cancer.

Dr. Dye moved that the sum of $60.00 be appropriated for expenses of the Committee on Control of Cancer. This motion was duly seconded and carried.

The report of the Council of the New England Medical Societies was then presented by Dr. Ralph W. Tuttle:

The Council of the New England State Medical Societies has had four meetings within the past year. The first meeting was held in Concord at the Snow Shoe Club on June 9, 1946. Aside from the delegates of the different State Societies there were the following guests: Dr. Robert O. Blood, Mr. James M. Langley, Mr. Frank J. Sulloway, Mr. George M. Putnam, Mr. Charles Gannon, Mr. Arthur J. Connors, of the American Federation of Labor, and Mr. Newell, member of the staff of the *Concord Monitor*.

Dr. Blood, chairman of the Committee on Maternal and Infant Care, gave an interesting account of the work of the committee in its educational program aimed at the reduction of maternal and infant deaths in the State.

Mr. James M. Langley, chairman of the State Hospital Study Commission, discussed the Hill–Burton Act.

Mr. Frank J. Sulloway, attorney for the Society, discussed methods of handling malpractice suits. He stated that the Society carries on a program of education to teach its members how malpractice suits arise and that three fourths of such suits are due to remarks of medical colleagues who do not know the full facts of the medical case. This education has been effective, as shown by the fact that the members of the Society have had the benefit of five successive reductions in the basic premium rate.

Mr. George Putnam, president of the Farm Bureau of New Hampshire and director of the National Farm Bureau, gave an interesting talk on the medical needs of the rural communities.

A representative of the American Federation of Labor was present at the meeting but did not address the group.

The topics for discussion at the next Council meeting were distributed as follows: public relations (Massachusetts); rural medical care (Vermont and Maine); prepaid insurance (Rhode Island); veterans (Connecticut); medical care (Rhode Island) and licensure (New Hampshire).

The next meeting of the Council was held in Boston at which the subjects stated were taken up. The secretary of the Council, Mr. Farrell, mailed the minutes of the previous meeting to all the members and also had the proceedings mailed and the report on Rural Health Care published in the *Rhode Island Medical Journal*. He sent to each member of the Council reports on the progress of the bills relating to medicine in the United States Senate and House of Representatives.

Dr. Tighe, representative from Massachusetts, reported on the question of medical public relations. He stated that the Council of the Massachusetts Medical Society had created a new position, Director of Medical Information and Education, and that this officer will be charged with organizing two divergent programs, a medical-education program and one designed to place that society in a more favorable light before the public. Several of the state medical societies have a full-time officer to publicize their activities. In some states he is a doctor, and in others a layman. It was stressed that public relations is an important part of our endeavor if we wish to maintain the practice of medicine throughout the country in its present form and keep out from under complete governmental control.

Dr. Metcalf reported on the seventh annual Congress on Industrial Health sponsored by the American Medical Association, this being the first time the congress has been held outside Chicago. Full co-operation was given by the Council to the American Medical Association and the Massachusetts Medical Society, which sponsored the meeting. The report of the scientific papers presented at the Congress has been published in the *Journal of the American Medical Association*. Programs distributed by the American Medical Association nationally carried us as cosponsor of the Congress.

After a discussion of the Kenny Foundation Campaign, Dr. Creighton Barker, of Connecticut, moved that it be the opinion of the Council of the New England State Medical Societies that the societies in this area should withhold approval of the Sister Kenny Foundation Public Appeal for funds in the opinion that it should secure its funds from already existing organizations to avoid duplication in programs for the control of poliomyelitis. This motion was accepted and unanimously adopted.

Dr. Pitts, president of the Rhode Island Medical Society, spoke on prepaid insurance and medical-care plans, which were discussed by the delegates from the several states.

Dr. Metcalf reported for the New Hampshire Society that the Blue Cross had 173,000 subscribers, the Blue Shield Surgical 68,000 and the Blue Shield Medical 15,000. At present the enrollment is much larger. The members from the other states were quite interested in this report. Maine has not done so well as some of the other states because there is more or less difficulty with the osteopaths. Maine is thinking of endorsing a private insurance carrier to write its medical insurance rather than the Blue Cross. The decision has not yet been made. Vermont has adopted the plan of the New Hampshire Physician Service and has formed an alliance with New Hampshire. Connecticut is still working out a program of its own, which will probably be somewhat similar to ours.

Dr. Cole Gibson, president of the Connecticut Medical Society, reported on the National Physicians Committee meeting in St. Louis. He discussed the work of the committee in Washington and called attention to the recent splendid publication put out by the committee under the title, *The Key to Collectivism*.

Dr. Miller, of Connecticut, inquired if any of the men present had any pronounced opinion concerning the situation whereby trustees of the American Medical Association have also served on the Board of Directors of the National Physicians Committee. There was rather a brief discussion of this point, and Dr. Metcalf called for a show of hands as to whether it was believed that there should be separation as regards such participation. The vote showed that nine signified that they believed the trustees of the American Medical Association should not also serve on the Board of Directors of the National Physicians Committee. There were no negative votes, but several members did not vote on the question.

The agenda for the next meeting included hospitals (New Hampshire), group practice (Connecticut), health education (Rhode Island), labor relations (Massachusetts), legislation (Vermont) and medical economics (Maine).

The third meeting of the Council was held in Boston in January. As usual there was an excellent attendance. Guests at this meeting were Drs. Frank J. Lawliss, Harold Q. Gallupe, John A. Bolster and John S. Wheeler, respective secretaries of the boards of registration in medicine in Vermont, Massachusetts, Rhode Island and New Hampshire and Dr. Leroy E. Parkins, chairman of 1946 Postgraduate Assembly, and Mr. Robert St. B. Boyd, executive secretary of the Massachusetts Medical Society.

There was a proposal from the Massachusetts Medical Society that the New England Postgraduate Assembly, hitherto sponsored by the Massachusetts Medical Society with the co-operation of the other New England medical societies, be sponsored by the New England societies through the Council of the New England State Medical Societies. After considerable discussion it was decided that the Council was not in a position to commit the different state societies to the sponsorship of the program without having approval from the respective societies. This is a problem that should be taken up by each of the medical societies for a report to the Council next year. The Massachusetts Medical Society will sponsor the New England Postgraduate Assembly this year as they have previously done, waiting confirmation by the different state medical societies as to whether they wish to co-operate with the Massachusetts Medical Society in sponsoring meetings in 1948.

Prior to the war the Assembly was held at Sanders Theater in Cambridge. No exhibits were permitted, but a nominal registration charge was made of persons attending the Assembly. The registration in 1941 was 699, and the total income was $2,828.25. A net profit of $301.41 was realized.

In 1946 the Assembly was renewed and was held at the Hotel Bradford, Boston. Exhibits were permitted. The total registration of physicians was 488. The income from exhibits was $3,600, and from registrations and tickets, $3,202.45. The total income was $6,802.45, and the total expense was $5,964.97. The net profit of $837.48 accrued to the Massachusetts Medical Society.

It is planned to hold the 1947 Assembly at the Copley Plaza Hotel, Boston, on October 29, 30 and 31. The ballroom, foyer, Colonial Room and Sheraton Room are to be used for exhibits and meetings. Possible income from exhibits is expected to be $4,500. (Forty-five registrations at $100 each.) Hotel rental charges are expected to be $1,115. Luncheons for two days and dinner for one evening will be at the regular charge to registrants. The registration fee for 1947 will be $2.00.

The question arises, Does the New Hampshire Medical Society wish to sponsor the Assembly?

Dr. Metcalf, reporting for the subcommittee of the Council representing the New Hampshire delegation on the subject of hospitals in the post-war world, read the following summary of a complete report submitted by the committee:

We suggest the following trend in hospitalization in the post-war world:

Expansion of the general hospital, with increasing acceptance of communicable diseases, of certain types of tuberculosis, of nervous and mental ailments and, perhaps in separate pavilions, of care for patients in the convalescent and chronic stages.

Increasing subsidies from the federal, state or county governments. The Hill–Burton Bill provides a subsidy. For "relief" patients the Government under its different programs pays only about 50 per cent of the actual cost of medical care; it should pay the entire cost for the patient so classified.

Extension of physical and occupational therapy.

State licensure for all institutions that care for the sick — supervised, we hope, by one agency.

Responsible boards of trustees who will co-operate with the medical staff and with a sure-fire administrator who has his feet on the ground.

Two groups of nurses, besides the graduates — the first group with better background and a longer train-

ing period, and the other, for the simpler tasks, with briefer training.

Higher wages for nurses and for all hospital personnel. The American Hospital Association is working on the problem of pensions. Social Security does its part, but it should be furthered by a fund contributed by the hospital and the employees themselves.

An increase in the number of doctors who have their offices in hospitals and an increase in group practice.

A gradual increase in the cost of hospital care, which will be materially alleviated by insurance plans.

Public-health centers in areas of scanty population, rather than an increase of small hospitals.

Closer co-ordination among hospitals, perhaps under the sponsorship of hospital councils.

In discussion Dr. Pitts reported that he had been informed that there had been no applicants for the new nursing class at Rhode Island Hospital that was to start in February, showing that the nursing situation promised to become critical.

Dr. Rice, of Massachusetts, discussed the program in that state for licensed attendants. Dr. Gallupe, secretary of the Massachusetts Board of Registration, stated that the board had approved eleven schools for licensed attendants with courses running from one year to eighteen months. He expressed the opinion that it was an excellent method to provide nurse auxiliaries. He further reported that Boston University was planning to inaugurate a five-year course in its new school program. Dr. Yeager, of Connecticut, stated that at a recent nurses' meeting in Hartford there had been much discussion of why nurses do not start training because of the conflict between nurses with college education and those with high-school training. He also reported that industry had attracted many nurses and nursing personnel.

Dr. Tighe, of Massachusetts, spoke on labor relations. He cited the two questions proposed: the advisability of meeting with labor leaders and the discussion of mutual problems regarding health and welfare. He recommended that for the time being action on a meeting be postponed. He amplified his reason with remarks off the record. He observed that it was the general belief of labor that industry should pay the costs of medical care, whereas industry considers the main expense involved in assisting in medical care for employees, other than inpatient plant service, to accept the cost of services involved for payroll deductions and so forth, to enable employees to purchase insurance, both from nonprofit and from casualty carriers. Dr. Welch remarked that one source of opposition from employers has been the fact that wage increases are known and publicized but that insurance benefits are not given equal publicity; hence, employers are not too favorably inclined to expand or to continue some of their programs now in operation.

Dr. Pitts spoke on health education. He reported that the subcommittee assigned to the topic had decided to concentrate on the matter of statewide health federations or councils under the sponsorship of the medical societies. Men from each state reported that there was some health-education plan in each of the different states. They believed that this subject should be taken up more fully by the state medical societies.

The subject of medical licensure was brought up. The secretaries of the boards of registration in medicine in Vermont, Massachusetts, Rhode Island and New Hampshire were present, following a meeting of their own in another room. The following report was submitted at this meeting, and as a result of the adoption of these regulations, licensure by endorsement will be possible in all the New England states except Maine, where the statutes prohibit it:

> The Rhode Island licensing authorities have given careful consideration to the possibility of establishing reciprocal relations with other New England states for the issuance of medical licenses. The Rhode Island Medical Board does not consider straight reciprocity advisable or permissible under the present medical act. The board has voted, however, to exempt any licensee from another New England state from the usual written examination, provided the requirements of the Rhode Island law are fully met by the individual applicant. Such candidates will be treated in the same manner as diplomates of the National Board of Medical Examiners. After evaluation of their credentials, they will be required only to appear before the Board of Examiners for an oral examination, which is actually more of an interview than an examination.
>
> It should be emphasized that the issuance of medical licenses by endorsement after oral examination is discretionary with the board. A licentiate who is not in good standing with the licensing authorities of his home state will, of course, not be considered. Also, Rhode Island will consider candidates for endorsement from only states that extend the same privilege to physicians registered in Rhode Island.
>
> Recently, the Rhode Island Board of Examiners in Medicine held a joint meeting with the Board Examiners in the Basic Sciences, and the latter will issue a certificate of ability in the basic sciences by endorsement after oral examination to candidates who meet the following qualifications:
>
> That he has passed in another state an examination in the basic sciences held before a board of examiners in the basic sciences or before a state board authorized to issue licenses to practice the healing art.
>
> That the requirements of that state are not less than those of Rhode Island so far as the basic-science subjects are concerned.
>
> That the board of examiners in the basic sciences of such state grant like exemption to persons holding Rhode Island certificates in the basic sciences.
>
> The fee for a certificate by endorsement would be the same as that for the regular examination — $10.00 in the basic sciences and $20.00 in medicine.

The fourth meeting of the Council was held at the Harvard Club of Boston on April 16, 1947, with the usual full attendance. Mr. John E. Farrell, the executive secretary, gave an excellent report of the activities of the year.

Dr. Metcalf called for discussion on the proposal of the executive secretary in his annual report for regional conferences of committees of the various state medical societies in this area on various problems concerned with medical economics. Dr. Miller, of Connecticut, suggested that copies of this report be submitted to Dr. Lull, secretary of the American Medical Association, with a request that he in turn submit it to the committee planning the Conference for County Medical Society Officers at the time of the American Medical Association meeting in June. He expressed the opinion that the idea of regional meetings should be incorporated in the discussion at this particular conference. He also stated that it might be advisable to have the various state societies in New England know of the desire of the Council of the New England State Medical Societies to assist them in educating their various committees in mutual problems regarding medical economics. This was discussed favorably by several members of the Council.

Dr. Metcalf summarized the opinion that the executive secretary should notify the secretary of each medical society regarding the desire of the Council to sponsor such conferences, and also to inquire whether the respective committees in the societies wished to participate at a meeting in the fall, possibly on the subject of medical public relations.

The executive secretary, in the absence of Dr. Rice, read his report regarding financing the Council, as follows:

> At present there seem to be two ways of raising funds for this Council. The first is in the way it has been done: by assessing each state society the same amount. Naturally, state societies with small memberships believe that they should not pay so much as state societies with larger enrollments. The second way would be to assess each state society an amount proportional to its membership roll. Again, quite naturally, state societies with large enrollments believe that they are carrying too much of the financial load. This method was tried a generation ago by an organization similar to this and came to grief over the issue.

There might be a third way. The Council hopes to take over the Postgraduate Assembly, conducted for several years by the Massachusetts Medical Society. Is there not reason to believe that this venture could be so managed as to yield enough profit to enable the Council to undertake further activities?

If this offer seems unwise, the conclusion is that this Council should raise its funds, as heretofore, by equal assessments from each state society.

Drs. Howard, O'Hara and Gibson entered the discussion and expressed the opinion that the Council should not branch out at this time. Therefore, Dr. Metcalf moved that the Council continue to finance its program as in the past, with each of the state medical societies contributing $100. Dr. Cole Gibson seconded the motion, which was unanimously adopted. It will be necessary for the House of Delegates to appropriate $100 for this purpose.

The president stated that a request would be sent to the Secretary of each of the medical societies requesting that official delegates be named at the time of the annual meetings of the various societies. Mr. Farrell called attention to the fact that it has been the policy to invite past delegates to attend all Council meetings, and he suggested that some official action should be taken in this matter.

Dr. Gibson moved that all former members of the Council of the New England Medical Societies be officially designated as honorary members and that they be invited to attend the meetings of the Council and, further, that from time to time such honorary members be communicated with to see if they wish to continue on the mailing list of the Council to receive notices and invitations of meetings. The motion was seconded and unanimously adopted.

The nominating committee submitted the following nominations for officers for the ensuing year: for president, Dr. Arthur H. Ruggles, Rhode Island; for vice-president, Dr. Stephen A. Cobb, of Maine; and executive secretary, Mr. John E. Farrell, of Rhode Island. Dr. Pitts moved that the nominations for officers be closed, the motion was seconded and approved. He then moved that the secretary be empowered to cast one vote for the slate as nominated. The motion was seconded and unanimously adopted.

Dr. Norman H. Gardner, of Connecticut, a member of the National Committee on Rural Medical Service of the American Medical Association, addressed the Council on the matter of planning for rural medical services by state medical societies. There was a general discussion of the subject. Dr. Gardner reported that the Connecticut State Medical Society planned to conduct a conference on rural health at Connecticut University at Storrs on July 16, and he requested that the Committee on Rural Health in each state society attend this conference. Mr. Ambrose B. Kelley, a former member of the Committee on Social Insurance of the National Association of Mutual Casualty Companies and a guest of the Council, commented on the procedure regarding the writing of insurance by private companies for persons living in rural areas, and stated that the private insurance companies cannot write the contracts on an individual basis at a low cost. He observed that the Grange in many communities works closely with the Farm Bureau and has served as an excellent outlet for the distribution of insurance. Dr. Metcalf reported in detail on the situation in New Hampshire, and Dr. Gardner closed the discussion by urging that each state have a rural-health committee to strengthen the work of the national committee so that it will be in a position to report that there was an active committee in every state concerned with the problem.

Dr. Reginald F. DeWitt, of Plymouth, New Hampshire, spoke on the subject of group practice in a small community. An interesting discussion followed.

Mr. Kelley spoke on the relation between the medical profession and the insurance companies and the problem of socialized medicine. In discussing national legislation he pointed out that the proponents of the Wagner–Murray–Dingell Bill had proved themselves better salesmen than the physicians, whose case may have been better and whose logic was probably irrefutable, but whose dramatization of the problem fell far short of that of the social planners, who appealed to the emotional phases of the entire issue.

Dr. Macmillan then stated that the Committee on Officers' Reports approved the report of the Committee to the Council of the New England Medical Societies and suggested that it be accepted.

The President observed that if the House of Delegates wished to approve the recommendation that the Council of the New England State Medical Societies sponsor the Postgraduate Assembly, it could report to the Council that it had done so but that each of the other states would have to act similarly before the Council could sponsor the assembly. He added that sponsorship would not entail any expense on the Society, unless for some reason the assembly which had heretofore been profitable, should fall far short. The Assembly would be better attended, if each state had its own sponsorship, instead of sole sponsorship by the Massachusetts Medical Society, and this course would probably make the Assembly much larger than it is at the present time.

Dr. Sullivan stated that sponsorship of the assembly by the New England Council would involve six hundred members and, if it were a success, even more. He asked for suggestions concerning where meetings could be held.

The Speaker observed that the assembly need not be held in New Hampshire and that some central city, such as Boston or Worcester, would be better able to accommodate the members.

A member inquired if the profits, if any, would accrue to the Council or to the Massachusetts Medical Society.

The President replied that profits would definitely accrue to the Council and that if the profits were large enough, the $100 supplied every year would no longer be necessary. He added that if the Council could become a concrete entity, which, in itself, might have a backlog after a few years, it could expand and do far more toward the promulgation of the good of the practice of medicine in all New England. He moved that the House of Delegates be empowered to vote in favor of the sponsorship of the new assembly. This motion was duly seconded.

The Secretary stated that the Assembly had always been held in Boston, with usually three or four hundred physicians from Massachusetts and a scattering from the other states. Last year, he added, there were 23 men from New Hampshire. He therefore believed that there would probably be a large attendance from Massachusetts, Connecticut and Rhode Island and that the meetings should be held in Massachusetts, perhaps in Boston. Consequently, the Massachusetts Medical Society would have to continue active support.

He then raised the question what would happen under the proposed sponsorship, if there was a deficit in any year. The assumption was, on the part

of the men from Massachusetts, that that deficit would be taken from the several New England medical societies, pro rata. In other words, the Massachusetts Medical Society would pay a larger proportion of the deficit than the New Hampshire Medical Society.

He assumed that the Massachusetts Medical Society would ordinarily run the meetings and that there would be a delegation from New Hampshire, which would be on the executive or sponsoring committee and would try to interest the men in New Hampshire in this meeting.

The Speaker then requested all those in favor of the motion to manifest assent by saying "Aye."

There was a chorus of "ayes," and the motion was carried.

The report of the Committee on Maternity and Infancy was then read, as follows:

This is the thirteenth year in which the New Hampshire Medical Society, through the Committee on Maternity and Infancy, has conducted a study of maternal and infant deaths during the previous calendar year. The study is conducted with the co-operation of the New Hampshire Department of Health, which gives the services of personnel in the divisions of Maternal and Child Health and Vital Statistics. All data are gathered by the Division of Maternal and Child Health, acting as agent for the Committee on Maternity and Infancy. Death reports are received in the Division of Vital Statistics and, after checking and coding of the causes recorded on the death certificates, are transmitted to the Division of Maternal and Child Health for follow-up information on each case. The members of the committee, it should be pointed out, do not know the identity of the patient, physician, hospital or community where the patient was delivered. It is important to point out that a study of this kind is made possible only through the co-operation of the reporting physicians, since decisions made are based entirely on the information at hand. The committee has endeavored, as in all past studies, to analyze openmindedly all information in each case that can be obtained and has attempted to appraise the data so far as possible, having the advantage of reviewing the events in retrospect and not admittedly being in the position of the physician in charge of the case, who must make his decisions on the spot. It is with this thought in mind that the committee wishes physicians to read the recommendations and suggestions made, with the hope that such comments as are made may be of value in the conduct of future cases presenting similar problems.

The committee wishes to emphasize the fact that this report and study are for the purpose of making available to the practicing physician information on maternal deaths and their causes. It is therefore essential that physicians respond as promptly as possible, giving as full information as they can on each case reported by them; this year, only two physicians failed to respond to the committee's request.

As a matter of record, the committee believes that the method of conducting this study should be described. After the data have been gathered, either through personal contact of a member of the Department of Health or by letter, the information is presented to the committee without identifying information. Each member of the committee has a copy of the report to study. A discussion of the details concerned with each case ensues. Then the decision of the committee is recorded. The committee classifies the causes of death in accordance with the facts. This classification may differ from that of the Division of Vital Statistics, according to the *International List of Causes of Death*. The only information that the Division has, of course, is the diagnosis of the physician recorded on the death certificate. The discrepancies in classification, therefore, are based on the fact that as the committee receives additional information the cause of death becomes more apparent. This year, for instance, there were 4 deaths reported as maternal deaths that the committee considered to be due to other causes, such as surgical shock and, in 2 cases, anesthesia. One death was believed to be due to self-inflicted poison.

Over the years during which these studies have been performed, there has been a real decrease in the maternal death rate. The committee would like to suppose that its efforts in indicating poor obstetric procedures to individual physicians is — in part, at least — responsible for this fact. Tables 1–5 present the causes of death and other data on maternal deaths since 1933.

TABLE 1. *Number of Maternal Deaths by Cause.*

CAUSE	NO. OF DEATHS ASSIGNED BY INTERNATIONAL LIST OF CAUSES OF DEATH	NO. OF DEATHS ASSIGNED BY COMMITTEE
Abortion (spontaneous, therapeutic or of unspecified origin), with mention of other infection	1	
Ectopic gestation, with mention of infection	1	1
Other and unspecified hemorrhage of pregnancy	1	1
Other toxemias of pregnancy	1	1
Other and unspecified hemorrhages of childbirth and puerperium	2	2
General or local puerperal infection (except pyelitis)	1	1
Puerperal thrombophlebitis	1	
Puerperal embolism and sudden death	1	1
Puerperal eclampsia	2	2
Other puerperal toxemias	3	2
Other specified conditions of childbirth	1	2
Other and unspecified conditions of childbirth and puerperium	1	1
Unknown		2
Totals	16	16

The committee further classifies the cases into four groups, as follows:

Group I. Cases in which the patient was at fault because of refusal of prenatal care, neglect, self-induced abortion and so forth (1 case).

Group II. Those in which the obstetric treatment was inadequate (2 cases).

Group III. Those in which death was apparently unavoidable (7 cases).

Group IV. Cases in which data were insufficient, and in which the cause of death was therefore undetermined (6 cases).

(It has been found that in some cases inadequate information frequently signified inadequate treatment.)

After the committee has made a decision in each case, including suggestions for conduct in the individual case, a letter containing this information is written to the reporting physician. It is hoped that this procedure will aid physicians in selecting the proper treatment for their patients. The committee fully realizes how much easier

TABLE 2. *Maternal Deaths according to County.*

COUNTY	URBAN	RURAL	TOTAL
Belknap	0	0	0
Carroll	0	0	0
Cheshire	0	0	0
Coos	1	0	1
Grafton	0	0	0
Hillsboro	8	0	8
Merrimack	2	0	2
Rockingham	0	0	0
Strafford	4	0	4
Sullivan	1	0	1
Totals	16	0	16

it is to decide the course of a case at a round table discussion than at the bedside at the moment when treatment is necessary.

In the study of maternal mortality by years it is interesting to note that the highest rate occurred in 1933, at about the time that the studies began. There has been a slowly receding rate through 1942, but in 1943 there was a rise in the rate, which remained stationary through 1944 and started to drop again in 1945. The rate in 1945 was 1.8 per thousand live births. The number of maternal deaths was 16, with a slight decrease in the number of births as compared with the previous year. There were 8551 births in 1945. In 1946, the year of this study, 16 maternal deaths were reported, and the birth rate reached an all-time high. The number of births reported was 11,489. This gives a maternal death rate of 1.4.

The committee is not discussing infant deaths or stillbirths in this report, but Table 3 presents the causes of death among infants under one year of age, and Table 4 a list of the chief causes of death in stillbirths. The committee would like to call attention to the number of infant deaths. It is believed that the accepted definition for a stillbirth should be restated in this report: the statistical definition adopted for use in the United States, and the one accepted by the Children's Bureau, the American Public Health Association, the Bureau of the Census and the one now in use in New Hampshire is as follows: "A fetus showing no evidence of life after complete birth (no action of heart, breathing or movement of voluntary muscle), if the twentieth week of gestation has been reached, should be registered as a stillbirth."

Maternal Deaths

During 1946 a total of 16 maternal deaths were reported. The number of births in the state was 11,489, giving the official rate on the basis of 16 deaths in terms of 1000 live births of 1.4. It is gratifying to the committee that the majority of the deaths were unavoidable; because of insufficient data, however, or no data at all, the committee has had to classify more maternal deaths as "undetermined" than in any previous years.

In the group of deaths for which responsibility was undetermined, it was interesting that there were 2 cases of inversion of the uterus. From what could be ascertained, both patients died of post-partum hemorrhage after the uterus had become inverted during the third stage of labor. This condition is admittedly a startling and sometimes dramatic situation. The committee wishes to suggest that no placenta should ever be delivered by a Credé maneuver unless one hand is between the fundus and the symphysis. If this procedure is observed, inversion of the uterus cannot occur. (By a Credé procedure is meant the squeezing of the uterus by the exertion of anteroposterior pressure and avoidance of downward pressure. Delivery of the placenta should not be attempted until it is obviously detached.) It is recognized by the committee that spontaneous inversions occur but also that every attempt should be made to avoid such a situation by warning against a forceful Credé and taking the precaution described above. In 1 case the committee believed that, although the physician described replacing the uterus, despite which bleeding persisted, the uterus may have been pushed back into the vagina without completely reducing the inversion.

The causes of other undetermined deaths were given as follows: chronic nephritis with premature delivery of six-month, stillborn twins and uremia with a stillbirth after which multiple infarctions were found in the liver and kidney with a complicating thrombophlebitis.

The group that the committee classified as unavoidable posed some interesting problems. These cases fell into two groups: death occurring from intrauterine or post-partum hemorrhage and toxemia of pregnancy. One of these cases was a woman of twenty-eight years of age who, during her fourth pregnancy, developed a sudden attack of acute lower abdominal pain that came and went at varying intervals. Examination during these attacks revealed nothing unusual, and although she had been admitted to a hospital for study, she was discharged twice with no findings. There was no external bleeding, and finally the patient in her last attack went into shock and expired. Autopsy revealed torsion of a five-month pregnant uterus filled with blood. The interesting fact in this case was that there was a history of a ventral fixation of the uterus several years previously; the patient, however, had gone through a normal pregnancy and delivery following that operation, and it is difficult to explain why torsion did not occur at that time but was the final cause of death in the later pregnancy. The committee believes that a ventral fixation, similar to the so-called "Kelley ventral fixation," should not be performed in the child-bearing age.

Again, in 1946, the leading cause of death in the cases studied was toxemia of pregnancy. In several cases it was noted that the treatment given to eclamptic patients was sodium chloride, or mention of glucose and hypertonic salts was made. The committee wishes to stress the fact that eclamptic patients should not be given sodium chloride and that early treatment of toxemia is imperative. One case of toxemia was charged to the patient, who did not appear for prenatal care but presented herself in labor with a high blood pressure, a +++ test for albumin in the urine and definite signs of toxemia. Even though the physician instituted immediate treatment with magnesium sulfate and hypertonic glucose and delivery was spontaneous, the patient died fourteen hours later. The committee repeats its recommendation concerning the treatment of toxemia — namely, that as soon as the condition has been discovered the patient be given magnesium sulfate; that early induction of labor be performed in accordance with the degree of prematurity; that glucose be given intravenously with magnesium sulfate in severe cases; and that oxygen and digitalization be employed in convulsive toxemias. It was of interest that the cases of toxemia reported in this series showed evidence of definite chronic nephritis or previous kidney damage. The committee doubted whether 1 case so reported was a

Table 3. *Infant Deaths under One Year of Age from All Causes.*

Cause	Male Infants	Female Infants	Total
Whooping cough	3	4	7
Septicemia and purulent infection (non-puerperal)	1	0	1
Influenza, without respiratory complications specified	2	1	3
Measles	1	0	1
Cancer of other and unspecified organs	0	1	1
Hemophilia	0	1	1
Meningitis (not due to meningococcus)	0	1	1
Convulsions (patient under five years of age)	1	0	1
Diseases of lymphatic system	0	1	1
Bronchitis, acute	0	1	1
Bronchitis, unspecified	1	0	1
Bronchopneumonia (including capillary bronchitis)	11	9	20
Lobar pneumonia	1	4	5
Pneumonia (unspecified)	4	3	7
Ulcer of stomach	1	0	1
Diarrhea and enteritis	14	10	24
Intestinal obstruction	1	0	1
Cirrhosis of liver, without mention of alcoholism	0	1	1
Peritonitis (cause not stated)	2	0	2
Acute nephritis	1	0	1
Congenital hydrocephalus	5	8	13
Spina bifida and meningocele	2	7	9
Anencephalus	2	2	4
Congenital malformations of heart	18	8	26
Congenital malformations of digestive system	2	2	4
Congenital malformations of genito-urinary system	1	0	1
Other and unspecified congenital malformations	8	1	9
Congenital debility (cause not stated)	3	1	4
Premature birth (cause not stated)	64	40	104
Intracranial or spinal hemorrhage	14	10	24
Other injuries at birth	7	2	9
Asphyxia (cause not specified), atelectasis	9	4	13
Other specified diseases peculiar to first year of life	10	3	13
Accidental mechanical suffocation	4	4	8
Accidental injury by fall	1	0	1
Obstruction, suffocation or puncture by ingested objects	0	1	1
Other and unspecified accidents	2	0	2
Sudden death	1	0	1
Ill defined	1	0	1
Unknown or unspecified	1	1	2
Totals	199	131	330

true toxemia, since the blood pressure was low and the signs not too clear cut. The committee believes that if permission for autopsy could be obtained in more of these cases, a definite diagnosis could be made; the fact that more autopsies are not performed is deplored.

The most striking fact concerning the type of cases studied this year was the lack of puerperal infections. There was only 1 case in which the mention of an infection was made. In this difficult case a young primipara, who had had a perfectly normal prenatal course and who had received excellent prenatal care, had a short tempestuous labor of three and a quarter hours and delivered a stillborn child. It was believed that these events indicated a premature separation of the placenta. The course that followed was tragically futile in that, despite every effort on the part of the physician and the consultants, the patient continued to bleed profusely and developed a postpartum infection. Every treatment, including the use

TABLE 4. *Chief Causes of Stillbirth according to Sex.*

CAUSE	MALE INFANTS	FEMALE INFANTS	TOTAL
Conditions in fetus, placenta and cord:			
Congenital malformations (incompatible with life)	13	31	44
Placental and cord condition	27	21	48
Birth injury (fetal death during labor)	7	3	10
Syphilis	0	1	1
Infection other than syphilis	0	0	0
Erythroblastosis foetalis	3	0	3
Other abnormality in the fetus	0	2	2
Conditions in mother associated with fetal deaths:			
Syphilis	1	2	3
Tuberculosis	0	0	0
Diabetes mellitus	0	1	1
Chronic disease of circulatory system	0	0	0
Chronic disease of genitourinary system	3	0	3
Other chronic disease	1	0	1
Other acute disease and conditions	2	0	2
Hemorrhage without mention of placental conditions	0	1	1
Toxemia of pregnancy	9	10	19
Infection	0	0	0
Difficult labor	3	5	8
Other accidents and violence	1	1	2
Ill defined and unknown	65	47	112
Totals	135	125	260

of penicillin, was given, and heroic efforts were made to control the infection and the bleeding. It was known that there was a lower uterine-segment laceration, as well as infection, and as a last resort the physicians decided on a hysterectomy, taking the chance of a fatal infection but realizing that anything less would probably result in a fatal hemorrhage. The patient did remarkably well after operation, but, despite transfusions and intensive treatment for the infection, she could not handle the infection enough to prevent the sloughing of the cervix, with hemorrhage, that finally caused her death about three weeks after operation. This case, because of its severity and possibly because of an individual resistance to the use of modern weapons against infection, is the exception rather than the rule. With the use of penicillin and the sulfonamides, the number of deaths due to infection has definitely decreased.

Another group of cases that deserve comment are those due to anesthesia. The importance of anesthesia during labor and delivery is emphasized; it is essential that a qualified anesthetist administer the anesthetic. The committee believes that a spinal or caudal anesthetic, when chosen, should be given only by qualified physicians trained in such technics.

The following opinion of the New England Society of Anesthesiology concerning the question of anesthesia may be of value to physicians in the consideration of the importance of anesthesia:

> It is the opinion of the New England Society of Anesthesiology that the administration of anesthesia is a form of medical practice.
>
> A thorough grounding in all stages of medicine is essential for the selection of the proper agent and method and for its safe administration.
>
> There are so many dangers inherent in all types of anesthesia that the success and safety of all the various methods is directly proportional to the experience and training of the person responsible. These dangers are so numerous and serious accidents are so imminent that it is imperative for a physician to be in constant attendance throughout the entire administration.
>
> Serious or potentially fatal complications are especially prone to occur during the course of intravenous anesthesia, spinal anesthesia and caudal analgesia. Since these accidents are usually preventable it is our opinion that a physician conversant with these dangers should be in constant attendance.

COMMENTS AND RECOMMENDATIONS

The committee wishes to state that adequate study and recommendations are possible only if the physicians in New Hampshire co-operate in the task of promptly presenting full data. This year, the study was made exceedingly difficult because of lack of response to the requests concerning the cases of maternal deaths reported. The data were either incomplete or lacking. Two physicians failed to respond at all. On the other hand, the majority of physicians who returned information did so completely and promptly.

It is recommended that intensive efforts to obtain permission for autopsy be made on the part of physicians after maternal deaths. This will usually assure a more accurate diagnosis and will thus avoid some of the discrepancies that occur in the final reporting of maternal deaths. It should eliminate to a large degree the element of guesswork in the final analysis.

The committee wishes to stress the importance of good prenatal care when patients present themselves early in pregnancy. It was noted that in some cases in which the patients were seen by the third month, physicians failed to do regular prenatal examinations. In at least 1 case of toxemia, the patient was allowed to go into convulsions without the institution of treatment. It is well recognized that many patients are careless about reporting to the physician early in pregnancy or are reluctant to admit their situation and to seek medical care. The committee wishes to recommend further that, when a physician is fortunate enough to have a patient seek his advice, he render the best possible prenatal care. The most important initial part of this care should consist of a complete physical examination, including laboratory tests, and a complete history, so that a thorough appraisal of the patient's past, present and future status can be determined.

The committee wishes to reiterate its recommendation that eclamptic patients be treated by the use of magnesium sulfate in the early stages, early induction with careful planning as to the stage of pregnancy, glucose and magnesium sulfate in severe cases and the use of oxygen and digitalization in convulsive toxemias. The administration of sodium chloride should never be condoned, and the drug should definitely be excluded from the therapy of toxemic patients.

The committee wishes to repeat its opinion concerning the importance of trained anesthetists. The training of physicians in the skill of anesthesia should be encouraged.

The committee wishes to comment on the apparent drop in the number of post-partum infections as a cause of death. It is hoped that with the continued use of penicillin and other modern weapons against infection this cause of death in maternity cases will be eliminated. It is recognized that individual cases present impossible problems owing to individual resistance or drug idiosyncrasies.

The committee wishes to encourage better record keeping on the part of physicians and hospitals. After a lapse of time, the type of record that is carried around in the head becomes of no value and cannot be used as a defense or safeguard for any purpose. Good records are a good investment for both the hospital and the physician.

The committee wishes to thank the physicians and hospitals that responded to their requests for information concerning maternal deaths and for the help they rendered in making this report possible. The committee will be happy to receive any recommendations or suggestions from the physicians throughout the state that may be helpful regarding these annual reports.

The committee wishes to acknowledge with appreciation the co-operation of the State Department of Health, through its divisions of Maternal and Child Health and Vital Statistics, in furnishing data and personnel in the preparation of this report.

TABLE 5. *Maternal Death Rates by Year (1933–1946).*

YEAR	RATE %
1933	6.3
1934	5.4
1935	6.1
1936	4.8
1937	4.3
1938	3.8
1939	3.1
1940	3.1
1941	1.9
1942	1.7
1943	2.7
1944	2.9
1945	1.8
1946	1.4

ROBERT O. BLOOD, *Chairman*
BENJAMIN P. BURPEE
JAMES SANDERS

Dr. Macmillan moved the acceptance of this report.

This motion was duly seconded and was carried.

Dr. Dube then presented the report of the Committee on Medical Economics, as follows:

New Hampshire Physician Service

The past year has been one of rapid expansion and development. The most important step taken has been the extension of the service to Vermont, with the transformation of the Corporation to the New Hampshire-Vermont Physician Service, effective last October. The membership of the Corporation and the Board of Directors and its subcommittees has been expanded to include representation from Vermont. The Vermont Medical Society has been active in enrolling its members, and an enthusiastic response has been made.

Since the program in Vermont is still in its initial stages, the figures given below refer almost exclusively to the New Hampshire Physician Service.

Growth in enrollment has continued at a gratifying rate. Of the forty-five medical-service plans in the United States that are associated with Blue Cross and have a total enrollment of 4,200,000, our own service now stands fourteenth in size.

There are at present, in round numbers, 110,000 subscribers to the Surgical Division, and of these, 40,000 are also enrolled under the Medical Division. It is interesting that the latter group, which increased at a much slower rate than the surgical in the first two years, is now expanding at approximately the same rate as the surgical.

Favorable loss ratios in both divisions have made possible an increase in benefits. There has been an upward revision of many items in the surgical schedule, and allowances for medical visits have been increased. The first step in preventive medicine has been taken with provision under the medical contract for allowances for immunization injections for infants under one year of age.

Veterans' Care

A highly significant development in the field of medical economics is the inclusion of the private physician in the program of medical care for veterans. The contribution of medical-school faculties under supervision of the dean's committees has made possible the present high standard of service achieved in Veterans Administration hospitals. A further step in the program is the utilization of the local physician in providing care for service-connected disabilities of the veteran. This arrangement is in effect in several states and is being presented for the consideration of this session of the House of Delegates.

This program is, of course, a form of so-called "government medicine." It is set up, however, in accordance with the principle previously advocated by the committee in discussing the relation of Government to medicine: the participation of the Government is confined to the economic aspects, and the physician is left in control of the professional relations. The committee therefore endorses this program and recommends its adoption by the New Hampshire Medical Society.

Senate Bill 545

Committee hearings are now being held on this bill. Proposed by Senators Taft, Smith, Ball and Donnell, it would establish a national health agency under which the various health activities of the federal government would be co-ordinated, would provide for the appropriation of $200,000,000 annually for assistance to the states affording medical, hospital and dental services for low-income patients, with provision for medical and dental examinations of school children; and would authorize specific funds for research in cancer and in dental diseases. A significant item in the bill is the permission specifically granted for utilization of nonprofit medical and hospital service plans in providing such care.

Many problems would arise in the administration of such a bill, the most serious one being the method of determining a person's eligibility for assistance. This presumably would have to be handled on the local level, as in relief cases, and it would be difficult to avoid the stigma of pauperization.

The committee approves the bill in principle, pending clarification of the details of administration.

L. K. SYCAMORE, *Chairman*
F. J. C. DUBE
R. W. ROBINSON

Dr. Johnston stated that he understood that administration of the procedures authorized by S. 545 was to be left up to the state and local authorities and moved that the Society determine who would be responsible for administration in the state and appoint a committee to take up this problem.

The motion was not seconded.

Dr. Sullivan stated that the bill under discussion was definitely socialistic, like other proposals, although it was couched in such terms that its socialistic tendencies were not quite so obvious as those of others proposed in Washington, adding that certainly, the method was clear if one looked into it deeply enough. Supporters of the bill stated that the administration of its provisions would be on the local basis, but the local administration of such a method would ultimately get back to Washington, the location of the head of the organization. He doubted whether any part of this bill were any better than those of any heretofore proposed.

Dr. Dye moved that, since the question of clarification was the only controversial point involved, the report be accepted.

This motion was duly seconded.

Dr. Richards believed that in trying to avoid federal interference with medicine, which many people considered inevitable, and at the same time voting to approve the bill under discussion, the Society would be acting in a contradictory manner.

Dr. Johnston stated that the bill was being passed quickly and that aid would be given to New Hampshire with the implementation of the bill, which was a grant in aid. He agreed that it constituted inter-

ference in medicine, but the bill assumed that local authorities would determine who is indigent. If the motion of Dr. Dye to accept the bill in principle were carried, a whole year would have passed before action, and this bill, in all probability, would have become law by then; the grant in aid to New Hampshire could not be implemented during that period.

The Speaker replied that the bill, of course, did not require endorsement by the Society.

Dr. Sullivan objected to the fact that the report of the Committee on Medical Economics ostensibly pertained to the Blue Cross and Blue Shield organizations in New Hampshire but also concerned the proposed bill in Congress. In other words, the proposal for approval of the committee's report, which comprised accolade for the Blue Cross and Blue Shield, also involved approbation of a socialistic piece of legislation. He thought that the two subjects should be separately discussed.

Dr. Dye stated that if passage of the bill were inevitable, the action of the House of Delegates would not change matters. Although he was opposed to socialized medicine, he understood that the various officers of the American Medical Association and the president of the National Hospital Association and others believed that this bill did not really infringe on the independent rights of physicians. If some sort of socialized medicine could not be avoided, the bill under discussion contained provisions that everybody wants; moreover, it offered an opportunity for local control of its administration. This particular seemed to be the least of a great many evils.

He therefore believed that the committee's report should be accepted, although he agreed that it should be voted on section by section. No definite federalized control of medicine, with compulsory employment of physicians and compulsory payroll deductions for everybody and a sort of panel system of medicine, like that in England, was envisaged in this bill.

The speaker made a point of order that the question before the House was the Senate Bill. Therefore, the motion would have to relate to the bill, rather than to the whole report.

Dr. Dye agreed with this statement.

Dr. Dinerman requested a recapitulation of the highlights of the bill under discussion.

Dr. Dube then read the portion of the report concerning the bill, adding that in his opinion the proposed legislation contained no more social medicine than was already in effect, in the care of the indigent in the towns, except that in the small towns inadequate care is often given. He compared the situation with that of old-age assistance, which could be regarded as a form of social medicine in that the beneficiaries would not receive the care unless the funds were granted in part by the state, town and federal governments. Before the inauguration of old-age assistance many older people went without medical care, because some of the town fathers refused to appropriate enough money to take care of these people adequately. The bill under discussion was apparently a grant-in-aid to take care of such cases as could not be cared for locally.

Dr. Feiner inquired whether anyone at the meeting had any knowledge of the reactions of Massachusetts and Vermont and other states to the bill and whether anyone knew how the National Physicians Committee had reacted to the bill. He added that although he believed that socialized medicine was inevitable, the House of Delegates did not have to approve it.

Secretary Metcalf stated that he did not know about the other New England states but that the Taft Bill had been approved by the National Physicians Committee and also by the American Medical Association. Senator Taft, he pointed out, had walked out on the hearings on the Wagner–Murray–Dingell Bill, which he considered to be socialism, and had promised to put in a bill to take the place of that bill. The result was the bill under discussion, which was proposed with the idea of avoiding the extreme socialism of the Wagner–Murray–Dingell Bill and for providing funds for the care of poor people in the different states, to be administered on a local basis. It was pointed out that the federal government had been giving New Hampshire grants for venereal control, tuberculosis control and other items for many years. The proposed legislation was simply an enlargement of what was already being done, as well as a counterattack, on the Wagner–Murray–Dingell Bill, on the assumption that if a bill of this sort goes through, there will be less likelihood of passage of the other legislation.

Dr. Brody observed that the severest critics of the American system of medicine were those who frequently brought up the fact that the indigent were not getting adequate care and that if the proposal legislation offered one way of stopping such critics that was the answer.

Dr. Dye recapitulated the advantages of the proposed bill, which he regarded as meriting approval, at least in principle.

After further discussion, the Speaker put the question, requesting all in favor of approving the report of the Committee on Medical Economics, in relation to S. 545, implying that the House of Delegates approves the bill in principle, with the reservation of desiring further elucidation of the methods of administration, to manifest assent by saying "aye."

There was a chorus of "ayes," with two dissenting votes, and the motion was carried.

The Speaker then pointed out that another item in the report required action — namely, the question of veterans' care by the local physician. He asked Dr. Metcalf to explain the question more fully.

Secretary Metcalf read the portion of his report concerning this subject, adding that, with the agreement and the fee table proposed by the Veterans Administration, he had sent to the secretary of each county society the following letter:

> A special committee appointed by the House of Delegates has formulated the enclosed agreement and fee schedule, which has been accepted by the Veterans Administration, for the care of veterans with service-connected disabilities. The fee schedule is divided into two parts: care in the home, office or hospital outpatient department of veterans with service-connected disabilities, and that of veterans with service-connected disabilities as inpatients in hospitals. Many patients in the second group will go directly to a Veterans Administration hospital. Some will be inpatients in a local hospital. The Veterans Administration will not be responsible in either group for medical or surgical bills, unless the illness is connected with war service.
>
> All members of the New Hampshire Medical Society are eligible to care for veterans under this agreement at these rates. The members who wish to do so should register with Dr. Drury, of Manchester, who will send a copy of the agreement and of the fee table and a letter of instructions.
>
> Please present these data at the next meeting of your county society. If you are not having a regular meeting soon, please consider the advisability of calling a special meeting.

Dr. Johnston observed that, in accordance with the letter, most delegates should be instructed by the county societies, and that it was the opinion of his society — Cheshire County — that that portion of the report should be accepted.

On a vote taken, Cheshire, Belknap, Carroll, Grafton and Rockingham counties accepted, and Strafford, Coos and Hillsborough counties rejected the recommendation.

Dr. Richards, explaining the rejection by the delegates from Hillsborough County, stated that the vote had not been taken until after a long scientific meeting and that some of the members who had left the room had expected to return and take part in the discussion. The president had wished to rush the matter through. The representatives of Nashua and Manchester had rejected the recommendation. Eighteen people had voted, and over a hundred had been present at the meeting. The Nashua County Society later met and expressed its approval of the recommendation.

The Speaker asked if anyone wished to make a motion.

Dr. Dube moved that the House of Delegates go on record as approving the fee schedule as given to the different county societies, as well as the program for the care of the veterans with service-connected disabilities.

This motion was duly seconded.

Dr. Dunbar pointed out that Hillsborough County had voted against the acceptance of the Veterans Administration fee list, not against the other proposal.

The Speaker then requested the delegates to signify approval or rejection of the program of hometown care for veterans.

There was a chorus of "ayes," with three dissenting votes, and the motion was carried.

The report of the Committee on Medical Education and Hospitals was then presented, as follows:

> The medical educational activities within the Society were practically eliminated, as would be expected, during the war period. The extension of fellowships granted us by the Commonwealth Fund in previous years were suspended for the duration, and there is no information available as yet regarding the fact or date of their resumption.
>
> The Speaker's Bureau — a list of volunteers for the presenting of papers for county meetings, and previously available to secretaries of county societies — is long since out of date. The membership — now fairly well stabilized after the war — is again being circularized for re-establishment of this list. It is hoped that this will stimulate some original presentations by our own membership, and such a list is welcomed by the county-society secretaries.
>
> In this connection the committee registers its support of the Society's Program Committee in its policy to arouse greater interest on the part of the members in presenting a greater portion of the program of the state meeting than they have in recent years. With the increasing numbers of younger men coming into the state, more emphasis should be placed on this phase of the program. Although prominent outside speakers are a necessary and valuable part of a state-society program, the main purpose should be the presentations of its members. Obviously, this can be accomplished only with a real interest and willingness on the part of the members.
>
> There have been many developments in the hospital situation in the past eighteen months — some of which have real significance for the future. This concerns the general implications of the participation of federal funds in hospital construction, which will in turn introduce similar participation in hospital standards and thereby, perhaps, an indirect participation in a program heretofore assumed to be under purely local control.
>
> In the summer of 1945, as previously reported, the Governor of New Hampshire appointed a commission for hospital survey. This followed Senate Resolution 191, which appropriated funds for such a survey in each state. The chairman of this committee served as a member of the commission, whose chairman was Mr. James Langley, of Concord. The survey, carried out by an efficient and experienced field worker, was completed in the fall of 1946, and the report submitted to the Governor.
>
> Two months ago two bills were introduced in the New Hampshire General Court, where they were referred to the Committee on Public Health and Appropriations. These are House Bills No. 370 and 371.
>
> House Bill No. 371 of the Revised Laws is an act to require the licensing, inspection and regulations of hospitals and related institutions. This act could encompass a wide range of activities and would require annual license. The "licensing agency" is the state health officer.
>
> This bill would set up a hospital advisory council to act with the state health officer. It is important that the same council would perform with the New Hampshire Department of Health in the administration of House Bill 370.
>
> Section 10 of House Bill 371 covers the origin of this hospital advisory council as follows:
>
> > The Governor with the advice and consent of the council shall appoint an Advisory Hospital Council to advise and consult with the Licensing Agency in carrying out the administration of this act. The Council shall consist of the head of the Licensing Agency (State Health Officer), who shall serve as chairman *ex-officio*, and eight other members, and shall include representatives of non-governmental organizations or groups, and of state agencies concerned with the operation, construction and utilization of hospitals, including representatives of the consumers of hospital services. Each member shall hold office for a term of three years, except that any member appointed to fill a vacancy occurring prior to the expiration of the term for which his predecessor was appointed shall be appointed for the remainder of such term and the terms of office of the members first

taking office shall expire, as designated at the time of appointment, three at the end of the first year, three at the end of the second year and two at the end of the third year after the appointment. Council members shall serve without compensation but shall be entitled to receive actual and necessary travel and subsistence expenses while serving away from their place of residence. The Council shall meet as frequently as the chairman deems necessary, but not less than once each year. Upon request by three or more members, it shall be the duty of the chairman to call a meeting of the Council.

House Bill No. 370 is an act relative to hospital survey and construction. Section 3, on administration, reads as follows:

> The Board of Health shall constitute the sole agency of the state for the purpose of (1) making an inventory of existing hospitals, surveying the need for construction of hospitals, and developing a program of hospital construction as provided in sections 6 and 7, and (2) developing and administering a state plan for the construction of public and other nonprofit hospitals as provided in sections 9 and 15 hereof.

The Hospital Advisory Council, as created under Bill 371, is "to advise and consult with the Board of Health in carrying out the administration hereof." The remainder of the bill has to do with procedures of application, review, approval and so forth.

In general, House Bill 370 is the implementation of the Hill-Burton Act for federal aid in hospital construction. This act will be administered by the United States Public Health Service on a state allocation basis through the agency of the state departments of health. Exhaustive national hospitalization surveys have been carried out by the Public Health Service. Allocation of funds to states will be based on a formula involving population, per-capita wealth and present hospital-bed availability. New Hampshire participation, as based on these factors, will be relatively small — $340,000 annually for the next five years.

It is assumed that administration of the act will involve practically some direct participation by the federal government by means of the United States Public Health Service in such matters as state boundaries affecting service areas of many of our institutions, which will involve the development of certain intrastate considerations.

Much could be written on the possible implication of this general movement. This is a brief sketch of the factual information.

JOHN P. BOWLER, *Chairman*
JAMES W. JAMESON
SAMUEL M. BROOKS

Dr. Macmillan then stated that the Committee on Officers' Reports approved this report and recommended it for consideration.

The motion to accept the report was duly seconded and was carried.

(*To be concluded*)

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33381

PRESENTATION OF CASE

A fifty-six-year-old man, formerly a lawyer, who had been employed for the previous seven years as a bartender, was admitted to the hospital with a complaint of weakness.

Eight years prior to admission the patient had noticed edema of the ankles following a venous ligation for varicosities. At about the same time he started drinking heavily, consuming about a quart of liquor a day. For about the same period he had experienced nocturia (two or three times). Six weeks before admission there was a rather sudden onset of dyspnea, which became so troublesome that he had to sleep sitting in a chair. He also became tense and shaky and stopped drinking alcohol after this episode. A physician, who had been giving him vitamins and liver extract for about a year, prescribed Purodigin about three weeks prior to entry. On the morning of admission, while still in bed, the patient was seized by a sharp pain in the left portion of the precordium that was aggravated by deep breathing on moving and relieved after a few hours by the application of heat.

Physical examination revealed a markedly dyspneic man who was slow in comprehending and inaccurate in answering questions. Many purpuric spots were present on the arms and abdomen. The skin was pale yellow. There was marked distention of the veins of the neck and legs. The cardiac impulse was felt 11 cm. to the left of the midsternal line in the fifth interspace. A loud apical systolic murmur was heard. The liver edge was palpable three fingerbreadths below the costal margin. There was pitting edema of the ankles.

The temperature was 100°F., and the blood pressure was 130 systolic, 100 diastolic.

Examination of the blood disclosed a red-cell count of 2,520,000, with a hemoglobin of 5.5 gm., and a white-cell count of 21,150, with 76 per cent neutrophils; the hematocrit reading was 24. Several nucleated red cells and macrocytosis and poikilocytosis were noted on the stained smear. Urinalysis revealed a specific gravity of 1.013 with a +++ test for albumin. The sediment contained 30 white cells and rare red cells per high-power field. The total serum protein was 6.1 gm. per 100 cc., with 2.6 gm. of albumin and 3.5 gm. of globulin. The nonprotein nitrogen was 220 mg., the serum calcium 4.6 mg., the phosphorus 12.6 mg., the phosphatase 8.2 units, the cholesterol 250 mg. and the cholesterol esters 151 mg. per 100 cc. The serum chloride was 92 milliequiv., and the serum carbon dioxide 7.1 milliequiv. per liter. The prothrombin time was 42 seconds (normal, 19 seconds). The cephalin-flocculation test was +++ in forty-eight hours. The

van den Bergh reaction was 1.4 mg. per 100 cc. direct and 2.2 mg. indirect. A blood Hinton test was negative.

X-ray films of the chest showed generalized enlargement of the cardiac shadow, the ratio being about 15:26. The aorta was somewhat tortuous, and there were mottled areas of increased density extending out into both lung fields from the hili. A plain film of the abdomen showed kidneys that appeared to be normal in size and position. The liver was somewhat enlarged. No unusual soft-tissue masses were noted, nor were any unusual areas of calcification seen. The visualized portions of the bones appeared normal. An electrocardiogram showed a rate of 75, a PR interval of 0.17 second, normal axis deviation and diphasic T waves in Leads 1 and CF_3. The T waves were low and upright in Leads 2 and 3 and inverted in Leads CF_4 and CF_5.

During the first thirty-six hours after admission the patient was practically anuric, passing only 75 cc. of urine, and 125 cc. was passed during the following twenty-four hours. The nonprotein nitrogen was 180 mg. per 100 cc., and the carbon dioxide 11 milliequiv. per liter. The patient became weak and vomited several times. On the fourth hospital day he was drowsy and the entire body became edematous. The blood pressure was 133 systolic, 95 diastolic. He expired quietly on the sixth hospital day.

Differential Diagnosis

Dr. John W. Zeller: When I first read this summary I thought that many of the data given indicated the presence of serious disease of the liver. On considering it further, however, I was more inclined to believe that the patient had declined rapidly because of renal and cardiac disease. Probably the strongest evidences in favor of liver disease are the history of alcohol and the presence of jaundice — I suppose that we can accept the yellow skin as representing jaundice; the record does not state that the scleras were yellow.

Dr. Benjamin Castleman: Can you answer that query, Dr. DuToit?

Dr. Charles H. DuToit: The scleras were yellow.

Dr. Zeller: The elevated bilirubin could have been present on the basis of prolonged elevated venous pressure and liver anoxia. According to the history, this condition persisted for no longer than six weeks, which I consider quite time enough for hepatic changes to have developed. There are other data here, however, that could perfectly well go with a diagnosis of severe primary liver disease. The liver was large, although that could be accounted for in other ways. There may have been changes in the vitamin K metabolism as evidenced by the presence of purpura and a prolonged prothrombin time. These findings, however. also occur in severe renal disease. The anemia could be explained in a clear-cut case on the basis of liver disease. A physician had been giving liver extract for a year previously, possibly with that in mind. The cephalin-flocculation test, of course, in itself is evidence more in favor of hepatic than of renal disease. The test, however, depends on alterations in globulin, which were present in this case and which also occur in renal disease. It alone probably argues somewhat in favor of liver disease. I am willing to concede that the patient had an abnormal liver, but I do not believe that it led to his rapid decline and death.

From the point of view of kidney disease we have the following pertinent data. It is stated that the patient had nocturia two or three times. That does not seem too important in view of the high alcoholic intake. The anemia is consistent with the anemia of prolonged renal disease, which may occur with either a high or a low color index. The urinary findings are not helpful because there was only one urine examination. It is obvious that the service that treated this man had a difficult problem, because he was comatose and not producing urine well and was certainly not a fit subject for adequate study. The high nonprotein nitrogen and the changes in the blood proteins are also consistent with severe renal insufficiency. The high serum phosphorus, the low calcium and the elevated phosphatase are probably the strongest group of findings that argue for primary renal disease of fairly long standing. How long, Dr. Castleman may be able to tell by the appearance of the bones, because if the condition persists for a sufficiently long time, secondary hyperparathyroidism may take place and actual bony changes typical of osteitis fibrosa result. The changes in the serum chloride and carbon dioxide are also consistent. The x-ray studies suggest the presence of pulmonary edema, which certainly would fit in with the picture of some type of cardiac or renal failure.

From the point of view of heart disease, it is evident that the acute episode that marked the beginning of the terminal illness was something that had to do with the heart or lungs. On the morning of admission the patient had chest pain for the first time, described as a sharp, precordial pain on the left side definitely aggravated by deep breathing and moving. It was relieved after a few hours by the application of heat. Certainly, it seems as if there was some pleural involvement, and the implication at the moment is that this man suffered an acute accident involving either the myocardium or the pericardium and the pleura. He showed definite evidence of elevated venous pressure, with distention of the neck veins, a large liver and edema of the legs followed by generalized edema. The cardiac findings themselves are indicative of a large heart.

So far as consideration of the accident that had taken place in the chest goes, there are not many data to help us in making a diagnosis. One wonders about coronary thrombosis. It seems to me that the white-cell count was too high to be explained purely on that basis, although it is a possibility. Any acute abdominal emergency with chest pain is quite unlikely from the rest of the story. We know, however, that in uremia it is possible for events of that sort to occur and not to be clearly defined clinically.

Dissecting aortic aneurysm is rather unlikely, although I was quite attracted to that diagnosis when I thought of the possibility of involvement of the renal arteries and subsequent oliguria. It would not entirely explain the blood chemical findings, however. The summary does not suggest anything resembling spontaneous interstitial pulmonary emphysema. Pulmonary infarction must be considered. This man had a prolonged prothrombin time, and the veins had been tied off eight years previously. We know that there are some disquieting cases in which venous ligation has failed to prevent pulmonary emboli, but I doubt whether that occurred in this patient.

Other conditions that sometimes occur in patients in terminal uremia are pericarditis with effusion or even septic pericarditis. In this particular case I believe that pericarditis may adequately explain the findings. The rapid onset of dyspnea about six weeks before admission might seem difficult to explain in this way, but cases of pericarditis with effusion and a fairly rapid onset of dyspnea occur. The pain on admission could have been due to pericarditis with some associated pleural involvement. I hope that the x-ray films will give some help on that.

So far as the blood pressure is concerned, a pressure of sufficient degree was maintained to make me doubtful about the presence of coronary thrombosis.

May I see the temperature chart? In the written abstract only one temperature reading of 100°F. is recorded. I should have expected a slightly higher temperature with a septic process. None are recorded, and the chart shows a gradual descent during the last three days in the hospital. The fact that the pulse came down is also interesting and is against the presence of uncomplicated myocardial failure. The respirations were steady — around 20— until they went up to a high figure shortly before death. It should again be pointed out that sometimes the temperature does not indicate the presence of sepsis in debilitated patients with uremia.

May we see the x-ray films?

Dr. Stanley M. Wyman: The enlargement of the heart described is well seen. I cannot say that it is a characteristic configuration. It might be due to pericarditis.

Dr. Zeller: Were the films taken in a recumbent position?

Dr. Wyman: No; the patient was upright.

There is no evidence of a large effusion in the pleural cavity, but I strongly suspect a small amount of fluid in each costophrenic angle. The mottled density in both lung fields seems to emanate from the hili and is patchy in character, suggesting edema.

The record states that in the film of the abdomen the kidneys are normal in size and shape. I believe that they are small and also that they are irregular in contour, suggesting lobulation. The liver may be large. The spleen I cannot make out. Dr. Zeller raised the question of bone changes, and I might say that the bones do look osteoporitic.

Dr. Zeller: That is a real help.

I do not feel like commenting to any great extent on the electrocardiogram. The findings are not particularly indicative of coronary thrombosis. The absence of Q waves is against it. The T-wave changes are consistent with a diagnosis of pericarditis.

Dr. DuToit: I might add that a pericardial friction rub was heard.

Dr. Zeller: That is also helpful. Is there any other information that I should have?

Dr. DuToit: No.

Dr. Zeller: From the point of view of the underlying renal disease, we now have an x-ray interpretation that indicates the presence of shrunken kidneys of some sort. So far as polycystic disease is concerned, I should not expect the kidneys to be shrunken and polycystic at the same time. Polycystic kidneys are usually fairly large. I should prefer to consider the presence of chronic glomerulonephritis, chronic vascular nephritis or pyelonephritis, with this picture as an end result. I doubt that the underlying disease was renal tuberculosis or some of the more definite urologic conditions with obstruction, ureteral or prostatic. In such a case I think that more definite information regarding such an obstruction would have been available during the patient's life.

Dr. DuToit: The patient was catheterized, and 75 cc. of urine was obtained.

Dr. Zeller: I rather doubt that the patient had an end stage of amyloid disease of the kidneys. I do not know on what basis it could occur. I have not heard of its occurring with cirrhosis of the liver.

For my final diagnosis I shall have to say that the patient had severe, diffuse, long-standing renal disease — probably chronic glomerulonephritis or chronic vascular nephritis — and pericarditis with effusion. The effusion may have been associated with some bleeding into the pericardium, which has often been described; I rather doubt that it was hemorrhage into the pericardium, however. I originally suspected a septic pericarditis, but since see-

ing the temperature chart, I am less impressed with that possibility. I also believe that this patient had pulmonary edema and secondary hyperparathyroidism, with evidence of osteitis fibrosa in the bones. I think that it is entirely likely that he had the alcoholic type of cirrhosis of the liver.

DR. WILLIAM W. BECKMAN: Do you care to comment on the blood smear? That bewildered us on the ward.

DR. ZELLER: I can comment to the extent of saying that I too am bewildered by it. I think that a smear of this sort can be associated with the anemia of severe liver disease. I was unable, actually, to find a description of anything like this to fit the picture of anemia associated with severe renal disease. If I were forced to say, I think that it is more consistent with severe liver disease than renal disease.

DR. JACOB LERMAN: The blood picture indicates bone-marrow invasion or blood loss.

DR. DUTOIT: Dr. Wyman Richardson saw the blood smear and said that it was suggestive of bone-marrow invasion such as multiple myeloma.

DR. BECKMAN: Was Bence-Jones protein found?

DR. DUTOIT: We were unable to find any by crude test.

CLINICAL DIAGNOSES

Uremia, due to chronic glomerulonephritis.
Hypertensive heart disease, with failure.
Portal cirrhosis of liver.

DR. ZELLER'S DIAGNOSES

Severe, diffuse, long-standing renal disease (? chronic glomerulonephritis or chronic vascular nephritis).
Uremia.
Pericarditis, with effusion.
Pulmonary edema.
Secondary hyperparathyroidism.

ANATOMICAL DIAGNOSES

Acute and chronic pyelonephritis.
Pericarditis, acute, fibrinous, uremic.
Cardiac hypertrophy.
Pulmonary congestion and edema.
Central congestion and necrosis of liver.
Hydrothorax, bilateral, slight.
Ascites, slight.
Parathyroid hyperplasia, secondary.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed an enlarged heart that weighed over 400 gm. There was pericarditis of the fibrinous type, with a little effusion — 75 cc. of turbid fluid — but no sepsis. I believe that it is rare to find septic pericarditis associated with uremia. One sees thick fibrin described as the bread-and-butter type, but cultures are almost always sterile. The coronary arteries were not remarkable. The kidneys were shrunken, weighing together 150 gm. They showed slight to moderate lobulation, the surface of the kidney between the scars being fairly smooth rather than coarsely granular. At the time of autopsy there were a number of wagers going on regarding what type of renal disease was present. The facts that the kidneys were lobulated and contained yellow areas and that the intervening parenchyma was smooth made one group think that it was chronic pyelonephritis; another group considered it vascular nephritis, and a third group, glomerulonephritis. Microscopical sections, however, revealed some degree of vascular change, but there was marked fibrosis and cellular infiltration throughout the kidneys, both chronic and acute. I believe that the whole process is best explained by chronic pyelonephritis, with some activity still going on. As a result of the long-standing renal disease there was secondary hyperplasia of the parathyroid glands. The bones showed a few areas of early bone resorption such as one might see in long-standing renal disease. The lungs were heavy, weighing over 1000 gm., and showed a fair amount of congestion and some edema. The liver was not enlarged, weighed 1400 gm. and on microscopical section showed a severe degree of central necrosis and congestion, such as one might see with failure of the right side of the heart; that is consistent with the engorgement of the neck veins, the pleural fluid — 200 cc. in each pleural cavity — and the ascites.

DR. BECKMAN: How about the bone marrow?

DR. CASTLEMAN: The bone marrow showed moderate red-cell hyperplasia.

CASE 33382

PRESENTATION OF CASE

A sixty-year-old nulliparous housewife entered the hospital with the chief complaint of weakness.

Six months before entry the patient had been admitted to another hospital complaining of weakness, nervousness and weight loss of unknown amount. She had had asthma for four years. The thyroid gland was somewhat enlarged, and the pulse was about 110. The basal metabolic rate was recorded at +40 per cent. An eosinophilia of 11 to 19 per cent was present. A thyroidectomy was advised, but the patient desired to delay the operation. Four months later, after being on iodine therapy, she was readmitted, and a subtotal thyroidectomy performed. The pathological report was "colloid goiter with no evidence of hyperplasia." Postoperatively, she was improved until ten days after discharge, when she awoke at 2:00 a.m. with "heaviness" of the right arm. This was followed in a few days by similar sensations in the left arm, the right leg and, finally, the left leg. Weakness

followed, and she became bedridden. Vitamin B injections did not help. No dysphagia was noted. Dyspnea and orthopnea became increasingly severe. No cough, chest pain or gastrointestinal symptoms were observed. Some mental deterioration had occurred gradually during the preceding two years. The patient had had nocturia (four times) without other genitourinary symptoms for several months. The menopause had occurred at the age of fifty-four years.

Physical examination revealed an emaciated, orthopneic woman with soft atrophic muscles. There was dependent edema of the arms, legs and sacrum. The heart rate was regular, with sounds of poor quality. The heart was not enlarged. There was flatness to percussion over the lower right portion of the chest, with diminished breath sounds but no rales. The liver edge was palpated four fingerbreadths below the costal margin. The abdomen was normal otherwise. The pupils and ocular movements were normal. There was no facial weakness. The palate and tongue were normal. Except for slight movement at the shoulder, there was complete paralysis of the right arm and hand. The strength of the left arm and hand was about a fourth normal. The dorsiflexors of both feet were paralyzed; there was little voluntary movement of the right leg; the left leg was somewhat stronger and could be raised voluntarily. The arm jerks were present on the right and absent on the left side, and the knee and ankle jerks were absent, as were the plantar reflexes. Because of the patient's mental status sensory examination was not satisfactory. Pinprick and touch were recognized everywhere but seemed to be diminished over the extremities. Vibration was felt at the wrists but not over the tibias and malleoli. There did not seem to be a sensory level. A healed thyroidectomy scar was present.

The temperature was 98.6°F., the pulse 120, the respirations 50, and the blood pressure 115 systolic, 75 diastolic.

Examination of the blood disclosed a white-cell count of 33,900, with 38 per cent eosinophils, 4 per cent lymphocytes, 4 per cent monocytes and 54 per cent neutrophils. The urine had a specific gravity of 1.018 and gave a ++ test for albumin but contained no sugar. Four red cells, 6 white cells and a rare granular cast per high-power field were present in the sediment. The urine culture showed colon bacilli and nonhemolytic streptococci. The total protein was 5.84 gm. per 100 cc., with an albumin-globulin ratio of 0.85. The nonprotein nitrogen was 35 mg. per 100 cc. An electrocardiogram showed a normal axis; the T waves were extremely low in Lead 1, flat in Leads 2 and 3 and upright in Lead CF_2. On the next day auricular fibrillation was noted.

X-ray studies showed moderate decalcification of the spine, an area of homogeneous density at the right base having the appearance of pleural fluid and a calcified area in the region of the right lobe of the thyroid gland.

The patient continued to suffer from dyspnea and orthopnea in spite of digitalis and oxygen. She became aphasic and disoriented and died on the sixth hospital day.

Differential Diagnosis

Dr. William Clark: It is not quite clear to me when the patient was admitted to this hospital, but I am assuming that it was about one and a half months after the onset of the sensation of heaviness in the right arm. I should like to separate the course of the illness into three phases, the first being characterized by asthma, the second by weakness, nervousness and loss of weight, and the third by neurologic, cardiac and renal disease. It seems reasonable to me, however, that one dominant pathologic process was responsible for all the manifestations and that the asthma was the first symptom. During the course of this illness a diagnosis of thyrotoxicosis was made, and a subtotal thyroidectomy was performed. In retrospect I believe that it is justifiable to question the diagnosis of hyperthyroidism in spite of the fact that it seemed a logical explanation for the weakness, nervousness, loss of weight and tachycardia prior to operation. Even in the presence of an elevated basal metabolic rate we know that such phenomena are common to many diseases, and fitting all three phases together will give us a more logical explanation for the preoperative symptoms.

The pathologist's report and the postoperative course make the diagnosis of thyrotoxicosis somewhat questionable. Some evidence of hyperplasia should have been found. It is my impression that complete involution of the thyroid gland is not the rule following iodine therapy. Extreme muscle weakness is sometimes encountered on the basis of Graves's disease, even after thyroidectomy, particularly when a large portion of the gland functions outside the neck and is not seen by the surgeon. I prefer to believe, however, that the patient did not have Graves's disease. During the early phases of the illness one might become immediately suspicious of periarteritis nodosa as a possible diagnosis because of the asthma and eosinophilia. The association of these two diseases has been pointed out by Dr. Francis M. Rackemann.* After the operation the patient seemed to have developed a neurologic disease and, in addition, presented fairly definite evidence of involvement of the heart and kidneys. I am referring, of course, to the orthopnea and dyspnea, pleural effusion, hepatomegaly and dependent edema in reference to the heart and to the urinary findings in reference to the kidneys. I shall

*Rackemann, F. M., and Greene, J. E. Periarteritis nodosa and asthma. *Tr. A. Am. Physicians* 54:112-118, 1939.

pass over the nervous-system involvement for a moment to make some remarks about the involvement of these two systems. Some of the respiratory distress may have been related to the asthma, although wheezing is not mentioned. The low serum protein may have played a role in the edema and may have been related to the liver disease. The pleural effusion could have been a manifestation of heart failure but also may have been associated with serositis. The renal disease consisted of albuminuria and cells in the sediment and perhaps the additional findings of a slight elevation of the nonprotein nitrogen and lowering of the serum protein. I note that there was no hypertension, and I should not consider the renal disease the primary factor.

Without going in detail into the findings in the examination of the nervous system, I shall assume that the only logical explanation is that a polyneuritis developed. The involvement was bilateral and somewhat bizarre, with rather definite sensory involvement.

Such neurologic manifestations are so frequently associated with periarteritis nodosa, occurring in the presence of asthma and a high eosinophilia, that they make such a diagnosis almost compelling. I shall attribute all the manifestations of the illness to a generalized necrotizing arteritis. Other causes of eosinophilia do not seem to fit well, and I shall not discuss them. Some criticism of the diagnosis of periarteritis nodosa may be justified on the basis of the lack of fever and hypertension, but we know that these findings are not always present. Periarteritis nodosa has strange manifestations, and tissue examination is almost always necessary to establish its presence. I should think that tissue removed at the thyroidectomy would not have been helpful in this regard. In addition, postmenopausal osteoporosis and generalized atherosclerosis were probably present, and the latter may have contributed to both the mental confusion and the heart disease.

Dr. Alfred Kranes: I was asked to see this patient after an episode of acute peripheral circulatory collapse characterized by marked tachycardia, a fall in blood pressure, sweating and dyspnea. It was at first thought that this represented an idiosyncrasy to barbiturates because a similar episode had occurred postoperatively, when barbiturates had been administered. Additional information in the history, however, ruled this factor out, since it was discovered that the patient had been taking these drugs intermittently for some time.

She was not more extensively studied because during her stay here she remained critically ill. I reached exactly the same conclusion that Dr. Clark did, believing that periarteritis nodosa was the best explanation for the complicated picture presented.

Clinical Diagnosis

Periarteritis nodosa.

Dr. Clark's Diagnoses

Periarteritis nodosa.
Pleural effusion.

Anatomical Diagnoses

Periarteritis nodosa.
Hydrothorax, bilateral.
Pericarditis, acute fibrinous.

Pathological Discussion

Dr. Benjamin Castleman: The diagnosis of periarteritis nodosa is not usually made grossly at autopsy because in most cases the involved vessels are arterioles and small arteries. It is only when the lesions are present in the larger arteries, such as the coronary and the mesenteric, that one can palpate or see the nodularity and beading of the vessel wall. In this case the only suggestive gross findings were some scattered whitish areas in the cortex of the kidneys and a yellowish spot in the interventricular septum. Microscopically, these foci proved to be small infarcts resulting from occluded diseased vessels. All stages of arteritis from acute necrosis of the vessel walls with polymorphonuclear — especially eosinophilic — infiltration to organization of thrombi with recanalization were seen in the heart, kidneys, liver, peripheral nerves and skeletal muscles.

The thyroid gland showed no evidence of hyperplasia or arterial disease. I was unable to find any arteritis in the lungs, but the bronchi contained a great deal of mucus and the basement membranes and muscle walls of the bronchi appeared thicker than normal. These findings are consistent with bronchial asthma.

Dr. Kubik will tell us about the neurologic findings.

Dr. Charles S. Kubik: When I saw the patient on admission the history of a sudden onset of the weakness of the right arm suggested a vascular lesion. The extent and nature of the motor and sensory involvement pointed to multiple lesions, and that together with a history of asthma, indications of cardiac disease and the presence of eosinophilia made the diagnosis of periarteritis nodosa extremely likely.

At autopsy nothing abnormal was observed in the brain, brain stem, spinal cord or peripheral nerves.

On microscopical examination there was arteritis involving a medium-sized subarachnoid artery of the medulla, although the medulla itself and the vessels within it were normal. In the middle and lower cervical regions of the spinal cord, at two neighboring levels, there were similarly diseased, small sub-

arachnoid arteries in the anterior, median fissure. One of these was probably occluded by thrombosis. There were no indications of infarction or signs of ischemia within the cord at these or other levels. The spinal nerves throughout were normal, and nothing abnormal was found in the cerebrum. The only abnormal finding observed within the central nervous system was axonal reaction of the anterior-horn cells of the cervical and lumbosacral regions of the spinal cord. This change, consisting of swelling and central chromatolysis, is characteristic of peripheral-nerve disease, and the reason for it in this case was quite obvious. There was extensive arteritis involving the small arteries of the peripheral nerves. None of the affected vessels were thrombosed. There was no actual degeneration of the nerve fibers; the myelin sheaths, although probably slightly abnormal, were essentially intact. It is interesting that there may be a marked axonal reaction even though visible changes in the nerve fibers are slight. The same thing has been true in some cases of infectious polyneuritis.

In the cases of periarteritis nodosa examined here, lesions of the nervous system have not been frequent. I recall another case in which there was severe disease of the peripheral nerves and at least one in which there were lesions of the brain.

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COST OF HOSPITAL CARE

The cost of hospital care, together with that of many necessities of life, has increased to a point where it can be met without sacrifice by only a small portion of the population. This is not surprising when it is realized that even in 1942, a war year, the average income of 84 per cent of the workers in Massachusetts was less than $3000 a year.[1] Two additional factors contribute to the difficulty: there is an acute shortage of hospital beds, and more and more people, owing to modern advances in the detection of such diseases as cancer, diabetes, nephritis and tuberculosis, require hospitalization. It is true that the cost of hospitalization can be completely or partially covered by enrollment in a prepayment insurance plan, but even the Blue Cross appears to be having trouble in meeting its obligations. Furthermore, although a patient is entitled to receive or able to pay for hospitalization, it is often impossible to secure a hospital bed, even in cases of emergency. The question arises, What can be done to relieve this situation?

In the first place, steps should be taken to increase screening tests whereby disease is detected before it has advanced to a stage that requires hospitalization and to educate the public regarding the symptoms and signs of various slowly progressive diseases. Much has already been accomplished along these lines in tuberculosis and diabetes, but a great deal remains to be done, both in these diseases and in others.

Secondly, certain types of patients should be encouraged, during the period of study and treatment, to remain in their homes or to take up residence in nursing homes, hotels and boarding houses. This ambulatory type of care is less expensive than hospitalization and can be conducted satisfactorily provided that adequate supervision is maintained by means of office visits or by attendance at outpatient clinics. In the latter, and occasionally in doctors' offices, group instruction offers an inexpensive type of medical care, having proved particularly effective in patients with tuberculosis, neuropsychiatric disorders and diabetes.

Thirdly, as previously mentioned in this column,[2] hospitals should be urged, at least while the acute shortage of hospital beds exists, to operate on a seven-day week, with service available in operating rooms, x-ray departments and laboratories. This would not only increase the number of available beds but also cut down somewhat on the per-diem cost, owing to the decrease in overhead charges that accompanies operation at full capacity. Furthermore, if personnel were available for this type of service, hospital care could be provided by existing hospitals at a lower cost per patient than could be attained by the construction of new hospitals.

Fourthly, when the patient has been admitted to the hospital, it should be the duty of the attending physician to limit hospital services to the indispensable minimum consistent with adequate study and care, to expedite treatment and to discharge the patient at the earliest possible moment that is

compatible with health. One hospital in Boston has adopted a plan whereby the total hospital charges of diabetic patients requiring medical and surgical care who were discharged during the previous week are shown at the staff visit each Monday. A typical sheet lists twelve ward and semiprivate patients with an average total charge of $269, exclusive of doctors' fees. Such a procedure should accomplish much in impressing on the physician the need for decision and action.

Finally, it is to be hoped that in the not too distant future the costs of the supplies and equipment that are essential to hospitals will drop to a reasonable figure. Just when this will occur, however, is a question on which the ablest economists refuse to hazard a guess. That this is the chief factor in the cost of hospital care is indicated by the fact that the cost of food, clothing, shelter, fuel and light has risen from a combined index number of 98 in 1941 to one of 149 in 1947.

Hospital costs, as well as the expenses of medical care, must be placed within the reach of all. Only with the co-operative efforts of physicians, hospitals, public-health agencies, organizations underwriting prepayment insurance and government — through full payment for services rendered to the indigent — can this goal be attained.

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1. McKittrick, L. S. Medical care in our free society. *New Eng. J. Med.* 236:921-927, 1947.
2. Editorial. Full utilization of hospital facilities. *New Eng. J. Med.* 236:767, 1947.

EPIDEMIOLOGY OF POLIOMYELITIS

ABOUT a year ago there was some discussion regarding the propriety and justification of criticisms in the lay press directed against the manner in which the public-health aspects of infantile paralysis were handled in one of Boston's suburbs.[1] This was merely one reflection of the limited knowledge concerning the causes of epidemics of this disease, the manner in which the causative virus spreads and the efficacy of measures intended to control its spread.

In a recent paper read at the Rocky Mountain Conference on Infantile Paralysis, Sabin[2] summarized some of the recent contributions to the knowledge of the epidemiology of poliomyelitis. His paper, in its published form, includes an appropriate and timely addendum in which he presents certain guiding principles that are suggested by the facts thus far accumulated. Practical public-health measures are then offered that are in accord with these principles. These suggestions should be helpful to health officers confronted with an outbreak of this disease.

Reduced to its barest essentials, the epidemiology of poliomyelitis may be considered to be similar to that of other enteric infections in which the causative virus is much more widely disseminated in the community during an epidemic than at other times. The care of patients and the public-health measures should therefore be directed toward limiting contact with and the spread of the virus. It has been shown that this virus is present for only a short time in the throat and more frequently and for a longer time in the intestinal tract and stools of certain apparently healthy people, as well as those of nonparalytic and paralytic cases during the epidemic. The virus may be transmitted to others by intimate contact, contaminated hands and fomites. Spread by the respiratory tract seems to play little if any role. The "filth" flies, however, can be contaminated with the virus and may spread it on to food in infective amounts. On the other hand, there is no evidence that the disease is spread by blood-sucking insects, since the virus is rarely found in the blood.

Some of the specific practical suggestions that Sabin offers in answer to the questions most frequently put to health authorities may be mentioned briefly as follows:

Measures designed to minimize spread by droplet infection do not seem to be warranted. It should therefore not be necessary to close motion-picture houses or churches or to refuse admission of patients with poliomyelitis to general-hospital wards.

The closing of playgrounds, swimming pools and other places where children come into direct contact with one another seems justified. The closing of schools depends on whether it is possible better to avoid contact between children in or out of school. Strenuous exercises are best

avoided during an epidemic, particularly by those who have had known and intimate exposure.

As to insect control, measures designed to minimize the contamination of food by flies in stores and in homes and efforts directed at the prevention of the breeding of flies where there may be any exposed sewage are warranted. The mass spraying of whole towns or communities with DDT, on the other hand, is of doubtful value.

Patients with poliomyelitis may be cared for on the wards of general hospitals provided that precautions similar to those used in caring for patients with typhoid fever are carried out, including the handling of their food, linens and excreta.

At home, patients with poliomyelitis should be isolated for at least two weeks, and even an isolation period of four weeks, dating from the first onset of symptoms, seems reasonable. The children of such households and the older members who are engaged in the handling of food in stores or restaurants or whose occupations bring them in intimate contact with children should remain at home for a period of at least two weeks. The same procedure is advocated for children who have been exposed in intimate play with members of an infected household.

Sabin emphasizes repeatedly that all these measures will probably not stop an epidemic, but in so far as they are carried out diligently, they may help at least some persons to escape infection who might otherwise be paralyzed.

It is to be borne in mind, however, that these conclusions and recommendations are based on Sabin's own interpretations of the results of recent experimental and epidemiologic studies. Other interpretations of the same findings are apparently possible and may cause some confusion in the minds of public-health workers. Dauer,[3] for example, concludes that the spread of the virus is probably through secretions of the oropharynx. His conclusion is based on the observations of a number of investigators that transmission of infection takes place in the interval between a few days before and a few days after the onset of a case, coupled with the fact that the virus has been recovered from oropharyngeal secretions in a large proportion of cases not longer than four or five days following the onset.

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3. Dauer, C. C. Incidence of poliomyelitis in 1946. *Pub. Health Rep.* 62:901-909, 1947.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

SIKORSKY — Vladimir N. Sikorsky, M.D., formerly of North Hampton, died on August 1. He was in his eighty-first year.

Dr. Sikorsky recently received a medal for fifty years of membership in the New Hampshire Medical Society.

Two daughters survive.

BOOK REVIEWS

Penicillin in Syphilis. By Joseph E. Moore, M.D. 8°, cloth, 319 pp., with 57 illustrations and 52 tables. Springfield, Illinois: Charles C Thomas, 1946. $5.00.

This book is almost as much a contribution to all general phases of medicine in which penicillin is used as it is an exposition of the specific treatment of syphilis. Anyone wishing to learn something about pharmacology and biology of penicillin can well spend his time with this concise analysis and interpretation of the work of the author, that of his immediate colleagues and that of the associated group studies. Slightly more than a third of the volume concerns the basic knowledge of penicillin; the rest deals with special problems of syphilis and how to combat them with penicillin.

Penicillin, like other specific antisyphilitic drugs, is capable of producing shock (the so-called "Herxheimer reaction"), and in early syphilis these reactions occur in at least 60 to 70 per cent of cases. Unlike the metallic drugs, however, there is no treatment fastness to penicillin. The danger of suppressive doses — as compared with total therapeutic doses — when penicillin is used for treatment of the disease associated with unrecognized early syphilis, is elaborately discussed. There is an excellent exposition of the relation between the time and dosage factors in the over-all treatment schedule. This important phase of the treatment of syphilis, which is well known to the syphilologist, is clearly expounded for those who will read carefully.

Weight for weight, penicillin is from two to four times as effective as Mapharsen in the therapy of syphilis in man. Its greatest effectiveness is in early syphilis, during the phase of the infection when the spirochetes are in their most active dividing phases. With an aqueous solution, a total dosage of 2,400,000 units, divided into sixty injections in seven and a half days, seems to be the best schedule for early active cases. It is strongly hinted, although not vigorously proposed, that ten daily single injections of 600,000 units of penicillin in peanut oil and beeswax is an even more effective schedule.

Gummas respond rapidly to penicillin; seroresistance of latent syphilis is not so responsive. Penicillin is so dramatically effective in preventing congenital syphilis that metallic therapy should be completely and universally replaced by penicillin therapy in pregnancy. The effect is equally dramatic in the management of the infant with congenital syphilis. In cerebrospinal syphilis, penicillin in addition to fever therapy is superior to all other treatment; alone, it is as effective as metal and fever therapy and is superior to any metal alone.

This small book is packed with information for the student of syphilis and contains essential material for those who treat syphilis.

Radiology for Medical Students. By Fred J. Hodges, M.D., Isadore Lampe, M.D., and John F. Holt, M.D. 8°, cloth, 424 pp., with 103 plates. Chicago: The Year Book Publishers, Incorporated, 1947. $6.75.

This monograph offers a basic approach to the problem of x-ray diagnosis and therapy, without attempting to provide

details in all the ramifications of radiology. The authors provide only a short discussion of the theory of the roentgen ray and brief descriptions of the apparatus, enough to make the theoretical concepts understandable. The technics of obtaining films are discussed only from the point of view of what one can expect to gain from the usual views of each region. The object of the book is not to make a roentgenologist out of each medical student who reads it, but rather to give him enough knowledge so that no matter whether he becomes a general practitioner or a specialist in any field, he will be able to utilize x-ray technic to its full extent and at the same time to recognize its inevitable limitations. The illustrations are ample in number and excellent in quality and follow along with the text so that they are easily available for study. About a third of the text is devoted to radiation therapy, which is rarely discussed in specific detail; rather, space is devoted to the general theoretical and clinical principles involved. For those who desire further information on any subject, an excellent bibliography follows each chapter. This is a book that every medical student would do well to own.

Whither Medicine: From dogma to science? By Antony Fidler, M.D. 12°, cloth, 115 pp. Edinburgh: Thomas Nelson and Sons, Ltd., 1946. 6 sh.

In this monograph the author, who is a docent of medicine of the University of Warsaw and is at present senior lecturer in medicine at the Polish School of Medicine in Edinburgh, offers a philosophical criticism and evaluation of the present scheme of what he terms "causal medicine." As an alternative, he suggests a system of diagnosis, prognosis and treatment called "the medicine of probability," based on analysis, by the experimental method, of comparative data from large groups of cases. He illustrates the application of this new scheme in medicine by examination of several thousand cases in seven tables in an appendix. His concept, contention and method seem those of the statistician rather than those of the clinician or physician; his paradoxical theory is interesting, but not immediately convincing. It may be questioned whether the medicine of probability would really be more scientific than causal medicine. Perhaps, in spite of the author's statements, medicine is still more an art than an exact science. He himself agrees that "the strength of the personal impressions of a physician grows with his experience, and that is perhaps why older physicians are more inclined to rely upon their clinical 'flair' than upon the results of laboratory findings, and it must be admitted that they are less often mistaken as to their patients' fate than those who place their faith in the findings of the laboratory."

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Charles Darwin and the Voyage of the Beagle. Edited by Nora Barlow. 8°, cloth, 279 pp., with twelve plates, 1 portrait and 1 map. New York: Philosophical Library, 1946. $3.75.

This biographical study is based on twenty-four small, informal unpublished notebooks of Darwin, and thirty-nine letters written by Darwin to his father and sisters, here published in their entirety for the first time. Eight of the letters were previously published in part in the *Life and Letters of Charles Darwin*, by Francis Darwin.

The first part is a short sketch of the life of Darwin, dealing especially with the incidents leading up to his joining of the Beagle expedition. The second part comprises the letters and notebooks. These personal notebooks, written mostly after working hours, throw an interesting light on Darwin's processes of thought. A good index concludes the volume.

Proceedings of the Charaka Club. Volume XI. 8°, cloth, 243 pp. New York: Richard R. Smith, 1947. $7.00.

This new volume contains a selection of papers read before the club during the years 1940 to 1944. Boston physicians are represented by five papers by Dr. Fred B. Lund, one in conjunction with Dr. Cecil K. Drinker. Lists of present and past members and unpublished material precede the papers. A number of the contributions are short biographical sketches of deceased members, including George L. Walton, by Dr. Lund, and Walter R. Steiner, by Dr. Rufus Cole.

Surgical Pathology. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), LL.D., F.R.S.C., professor of pathology, University of Toronto. Sixth edition. 8°, cloth, 858 pp., with 530 illustrations, including 22 in color. Philadelphia: W. B. Saunders Company, 1947. $10.00.

This authoritative textbook, first published in 1925 and last revised in 1942, has again been revised. A new section has been added on the pathology and pathologic physiology of congenital heart disease. New material includes tumors of the larynx, pinealoma, Bittner's milk factor in relation to breast cancer, avitaminosis in cancer of the mouth, the Papanicolaou vaginal-smear method in the diagnosis of carcinoma of the cervix, fibrous dysplasia of bone, inflammatory nodules in chronic arthritis and fibrositis of the back. The book is recommended for all medical libraries and as a standard text on the subject.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 25

FRIDAY, SEPTEMBER 26

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, SEPTEMBER 29

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, SEPTEMBER 30

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, OCTOBER 1

*12:00 m. Grand Rounds and Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

SEPTEMBER 23. Norfolk District Medical Society. Page 382, issue of September 4.

OCTOBER 3 AND 4. New York Academy of Sciences. Page 348, issue of August 28.

OCTOBER 6–10. American Public Health Association. Page 456, issue of March 20.

OCTOBER 6–17. New York Academy of Medicine. Page 348, issue of August 28.

OCTOBER 9. Practical Points in Geriatrics. Dr. Roger I. Lee. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER–DECEMBER. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

OCTOBER 13–18. Medicolegal Conference and Seminar for Pathologists, Medical Examiners and Coroners. Page 242, issue of August 14.

OCTOBER 29–31. New England Postgraduate Assembly. Copley Plaza Hotel, Boston.

FEBRUARY 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

APRIL 19–23. American College of Physicians. Page xiii, issue of July 31.

MAY 6–8. American Association for the Study of Goiter. Page xiii, issue of July 31.

MAY 11–15. American Association on Mental Deficiency. Page 140, issue of July 24.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX EAST

SEPTEMBER 24.
NOVEMBER 19.
JANUARY 21.
MARCH 24.
MAY 12. Annual meeting.

All meetings will be held at the Bear Hill Golf Club.

NORFOLK

SEPTEMBER 23. Boston University Night.
OCTOBER 28. Lahey Clinic Night.
NOVEMBER 25. Tufts Night.
JANUARY 27. Round-Table Discussion: Bleeding from the Alimentary Tract.
FEBRUARY 24. Obstetric and Gynecologic Night.
MARCH 23. Harvard Night.

(*Notices continued on page xvii*)